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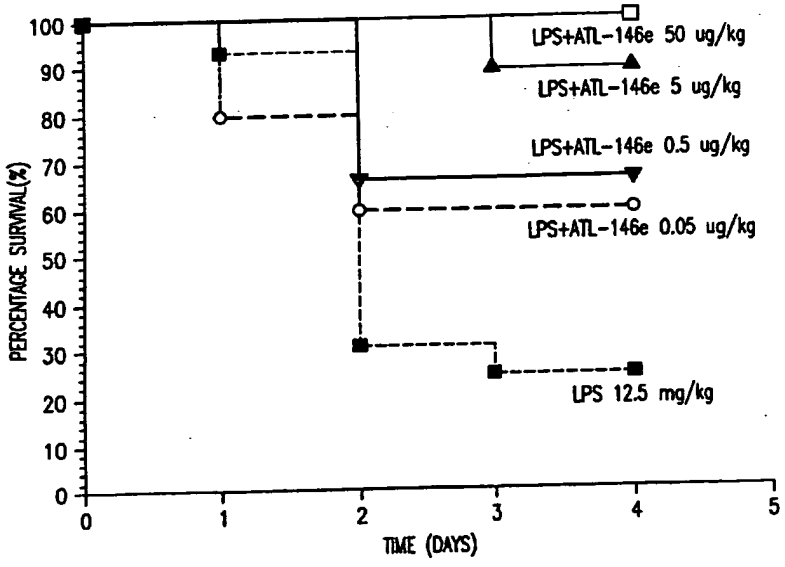
(54) Title: USE OF A2A ADENOSINE RECEPTOR AGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASES



(57) Abstract: The present invention provides a therapeutic method for treating biological diseases that includes the administration of an effective amount of a suitable antibiotic agent, antifungal agent or antiviral agent in conjunction with A_{2A} adenosine receptor agonist. If no anti-pathogenic agent is known the A_{2A} agonist can be used alone to reduce inflammation, as may occur during infection with antibiotic resistant bacteria, or certain viruses such as those that cause SARS or Ebola. Optionally, the method includes administration of a type IV PDE inhibitor

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USE OF A2A ADENOSINE RECEPTOR AGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASES

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Cross-Reference to Related Applications

This application claims priority from U.S. provisional patent application Serial No. 60/371,434, filed April 10, 2002, and U.S. provisional patent application Serial No. 60/387,184, filed June 7, 2002, both of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides a method for treating inflammation caused by bacterial, fungal or viral infections and the inflammation caused by the treatment of these infections, *e.g.*, by the death of the bacterial or viral cells.

BACKGROUND OF THE INVENTION

Bacterial, fungal and viral pathogens can cause infections which can lead to severe illness and even death. For example, the spore-forming Gram-positive rod *Bacillus anthracis* causes anthrax, a worldwide disease primarily affecting herbivores. Human infections occur sporadically from contact with

infected animals or contaminated animal products. The disease is a constant threat in endemic regions because spores can persist for years in the soil. Recent events in the United States underscore the potential of anthrax as a bioterrorism agent.

The pathogenisis of lethal infections is complex, requiring germination of the spore inoculum, systemic invasion, multiplication, and toxin production leading to death. Often the symptoms of infections can include development of fatal inflammatory (septic) shock. Thus, adjunctive therapies to minimize the detrimental effects of inflammatory shock are under active investigation.

Inflammatory shock can be caused by the pathogens directly or by the death of the pathogens after treating the patient with a drug that kills the pathogen. Often, the sudden development of fatal inflammatory (septic) shock and the progression of the disease, despite the availability of a bacteriological or antiviral cure, account for the high mortality from these pathogens.

The inflammatory shock can be caused by the bacteria, fungal or viral pathogens directly or from the treatment thereof, *i.e.*, the death of the pathogens due to treatment with antibacterial, antifungal or antiviral agents. Agonists of A_{2A} adenosine receptors inhibit inflammation caused by dying pathogens. Accordingly, there is a need for selective, potent, and specific A_{2A}AR agonists for use in adjunctive therapy for treating inflammatory bacterial, fungal and viral infections.

In accordance with the present invention, selective, potent, and specific A_{2A}AR agonists have utility as a potential adjunct in therapy for treatment in combination with other agents that kill bacterial, fungal and viral infections such as, for example, anthrax, tularemia, escherichia coli and plague.

There is currently a need for pharmaceutical agents that are useful to reduce an inflammatory response due to the invasion of bacteria, funguses, or

viruses or to reduce the inflammatory response due to toxins released by the bacteria, funguses, or viruses while alive or after they are killed using antibacterial agents, anti fungal agents or antiviral agents.

SUMMARY OF THE INVENTION

The present invention provides a therapeutic method for treating biological diseases that includes the administration of an effective amount of a suitable antibiotic agent, antifungal agent or antiviral agent in conjunction with an A_{2A} adenosine receptor agonist. If no anti-pathogenic agent is known the A_{2A} agonist can be used alone to reduce inflammation, as may occur during infection with antibiotic resistant bacteria, or certain viruses such as those that cause SARS or Ebola. Optionally, the method includes administration of a type IV PDE inhibitor. The A_{2A} adenosine receptor agonist can provide adjunctive therapy for treatment conditions such as, the inflammation, caused by sepsis, for example, *human uremic syndrome* when administered with antibiotics in the treatment of bio-terrorism weapons, such as anthrax, tularemia, Escherichia coli, plague and the like. The present invention also provides adjunctive therapy for treatment of lethal bacterial, fungal and viral infections such as anthrax, tularemia, escherichia and plague comprising administration of an antibacterial agent, an antifungal agent or an antiviral agent in conjunction with selective, A_{2A} adenosine receptor agonists.

The present invention provides a therapeutic method for treating biological diseases that provoke inflammation either alone or in combination with a disease killing medicine. These include bacteria in combination with antibiotics, including but not limited to bacteria that cause anthrax, tularemia, plague, lyme disease and anthrax. Also included are viruses including but not limited to those that cause RSV, severe acute respiratory syndrome (SARS),

influenza and Ebola with or without anti-viral therapy. Also included are yeast and fungal infections with or without anti-yeast or anti-fungal agents.

The antibacterial agent, antifungal agent or antiviral agent can be co-administered (*e.g.*, simultaneously) with the A_{2A} adenosine receptor agonist or they can be can be administered either simultaneously or as a mixture or they can be administered subsequently. The subsequent administration of the A_{2A} adenosine receptor agonists can be prior to the agent, within minutes or up to about 48 hours after the administration of the agent. Preferably the administration of the A_{2A} adenosine receptor agonists will be within about 24 hours and more preferably within about 12 hours.

The method of the invention will also be useful for treating patients with sepsis, severe sepsis, and potentially, the systemic inflammatory response syndrome, in addition to septic shock. The A_{2A}AR agonists exert multiple anti-inflammatory effects early in the inflammatory cascade, and thus a short course of an A_{2A}AR agonists could produce profound benefit in serious, life-threatening infectious and inflammatory disorders of humans, including inhalational anthrax, tularemia, escherichia and plague.

The anti-inflammatory effect of A_{2A}AR agonists has been documented *in vivo*, in experimental models of meningitis, peritonitis and arthritis. The potentially fatal syndrome of bacterial sepsis is an increasingly common problem in acute care units. Sepsis and septic shock, now the eleventh leading cause of death in the United States, are increasing in frequency. Current estimates indicate that about 900,000 new cases of sepsis (approximately 60% Gram negative) occur in the United States annually with an estimated crude mortality rate of 35%. Furthermore, the mortality rate, as assessed in recent clinical trials, is approximately 25%, while approximately 10 % of patients die from their underlying disease. Shock develops in approximately 200,000 cases

annually with an attributable mortality rate of 46 % (92,000 deaths). Sepsis accounts for an estimated $ 5-10 billion annually in health care expenditures. It is now widely appreciated that among hospitalized patients in non-coronary intensive care units, sepsis is the most common cause of death. Sepsis syndrome is a public health problem of major importance. A_{2A}AR agonists are anticipated to have use as a new and unique adjunctive therapeutic approach to reduce morbidity and mortality. It is believed that this treatment will improve the outcome in systemic anthrax, tularemia, escherichia and plague.

The agonists of A_{2A} adenosine receptors of the invention can inhibit neutrophil, macrophage and T cell activation and thereby reduce inflammation caused by bacterial and viral infections. The compounds, in conjunction with antibiotics or antiviral agents can prevent or reduce mortality caused by sepsis or hemolytic uremic syndrome or other inflammatory conditions. The effects of adenosine A_{2A} agonists are enhanced by type IV phosphodiesterase inhibitors such as rolipram.

The invention also provides a compound of formula I for use in medical therapy (*e.g.*, for use as an adjunct in the treatment of potentially lethal bacterial infections, such as, anthrax, tularemia, Escherichia, plague, or other bacterial or viral infections, and treatment of systemic intoxification caused by bacterial and/or viral infections, as well as the use of a compound of formula I for the manufacture of a medicament for reducing inflammation caused by the bacteria or virus or the treatment thereof in a mammal, such as a human. The compounds of the invention are also useful for treatment of treating systemic intoxification wherein the bacterial or viral agents cause inflammation either directly or as a result of treatment, *e.g.*, with an antibiotic or antiviral agent.

Sepsis is a severe illness caused by overwhelming infection of the bloodstream by toxin-producing bacteria or viruses. The infection, which can

manifest as inflammation, can be caused by the bacteria or virus pathogens directly or from the treatment thereof, *i.e.*, the death of the pathogens due to treatment with antibacterial or antiviral agents. Sepsis can be also be viewed as the body's response to an infection. The infection can be caused by micro-organisms or "germs" (usually bacteria) invade the body, can be limited to a particular body region (*e.g.*, a tooth abscess) or can be widespread in the bloodstream (often referred to as "septicemia" or "blood poisoning")

The systemic intoxification or inflammatory shock is often referred to as Septic shock; Bacteremic shock; Endotoxic shock; Septicemic shock; or Warm shock.

Septic shock is a serious, abnormal condition that occurs when an overwhelming infection leads to low blood pressure and low blood flow. Vital organs, such as the brain, heart, kidneys, and liver may not function properly or may fail. Septic shock occurs most often in the very old and the very young. It also occurs in people with underlying illnesses. Any bacterial organism can cause septic shock. Fungi and viruses may also cause this condition. Toxins released by the bacteria, fungi or viruses may cause direct tissue damage, and may lead to low blood pressure and/or poor organ function. These toxins can also produce a vigorous inflammatory response from the body, which contributes to septic shock.

In another aspect, the present invention also provides a method to treat severe acute respiratory syndrome (SARS), comprising administering to a mammal in need of said therapy, an effective anti-inflammatory amount of an agonists of A_{2A} adenosine receptor, optionally with a PDE-IV inhibitor, such as, rolipram.

DESCRIPTION OF THE FIGURES

Figure 1 illustrates the dose dependent response from the $A_{2A}AR$ agonist ATL146e (ATL) and protection of mice from E. Coli 026:B6 LPS-induced endotoxemia. The mice were treated with IP injection of the indicated doses of ATL one hour prior to LPS (12.5 μg/kg) and at 6 hour intervals for a total of 8 doses/48 hours.

Figure 2 illustrates the doses dependent response of ATL146e (DWH) on survival of mice treated with LPS. The treatment schedule is the same as in Figure 1.

Figure 3 illustrates that the $A_{2A}AR$ agonist ATL146e (ATL) protects mice from LPS-induced endotoxemia after a delay in the onset of therapy. Animals were treated with LPS and ATL146e (50 μg/kg) as in Figure 1 except that the first treatment with ATL was delayed for the indicated period of time.

Figure 4 illustrates that the $A_{2A}AR$ antagonist ZM241385 (ZM) inhibits protection by ATL146e (ATL) in mice treated with LPS.

Figure 5 illustrates that the $A_{2A}AR$ agonist ATL146e provides less protection to $A_{2A}AR$ KO mice, relative to wild type mice, from *E. coli* 026:B6 LPS-induced endotoxemia.

Figure 6 illustrates that ATL146e (ATL) increases survival of mice injected with live E. Coli. and treated with an antibiotic (ceftriaxone) compared to mice treated with antibiotic alone. All mice were injected with 20 million E. Coli IP at time 0. Where indicated mice were treated once at time 0 with ceftriaxone or with 50 μg/kg ATL146e 8 times at 6 hour intervals..

Figure 7 illustrates the reduction of the Renal IL-6 in mice exposed to LPS/Stx2 for 6 hours using ATL-146e and ATL-203.

Figure 8 illustrates the reduction of chemokine Renal RANTES in kidney samples in mice exposed to LPS/Stx2 for 6 hours using ATL-146e and ATL-203.

Figure 9 illustrates the reduction of infiltration of neutrophils in kidneys of C57BL/6 mice using ATL-203.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are used, unless otherwise described. Halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, aralkyl, alkylaryl, etc. denote both straight and branched alkyl groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl includes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C_1-C_4)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

It will be appreciated by those skilled in the art that the compounds of formulas (I), (II), (III), and (IV) have more than one chiral center and may be isolated in optically active and racemic forms. Preferably, the riboside moiety of the compounds is derived from D-ribose, i.e., the 3′,4′-hydroxyl groups are alpha to the sugar ring and the 2′ and 5′ groups is beta (3R, 4S, 2R, 5S). When the two groups on the cyclohexyl group are in the 1- and 4-position, they are

preferably *trans*. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, or enzymatic techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine adenosine agonist activity using the tests described herein, or using other similar tests which are well known in the art.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C_1-C_8)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, heptyl or octyl. As used herein, the term "cycloalkyl" encompasses bicycloalkyl (norbornyl, 2.2.2-bicyclooctyl, etc.) and tricycloalkyl (adamantyl, etc.), optionally comprising 1-2 N, O or S. Cycloalkyl also encompasses (cycloalkyl)alkyl. Thus, (C_3-C_6)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. (C_1-C_8)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C_2-C_6)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, or 5-hexenyl; (C_2-C_6)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, or 5-hexynyl; (C_1-C_6)alkanoyl can be acetyl, propanoyl or butanoyl; halo(C_1-C_6)alkyl can be iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl,

2-fluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; hydroxy(C_1-C_6)alkyl can be hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 4-hydroxybutyl, 1-hydroxypentyl, 5-hydroxypentyl, 1-hydroxyhexyl, or 6-hydroxyhexyl; (C_1-C_6)alkoxycarbonyl (CO_2R^2) can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, or hexyloxycarbonyl; (C_1-C_6)alkylthio can be methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, or hexylthio, (C_2-C_6)alkanoyloxy can be acetoxy, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, or hexanoyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyraxolyl, pyrrolyl, pyrazinyl, tetrazolyl, puridyl (or its N-oxide), thientyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl denotes a radical of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and 1, 2, 3, or 4 heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, (C_1-C_8)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

The term "heterocycle" generally represents a non aromatic heterocyclic group, having from 3 to about 10 ring atoms, which can be saturated or partially unsaturated, containing at least one heteroatom (*e.g.*, 1, 2, or 3) selected from the group consisting of oxygen, nitrogen, and sulfur. Specific, "heterocycle" groups include monocyclic, bicyclic, or tricyclic groups containing

one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. A "heterocycle" group also can include one or more oxo groups (=O) attached to a ring atom. Non-limiting examples of heterocycle groups include 1,3-dioxolane, 1,4-dioxane, 1,4-dithiane, 2*H*-pyran, 2-pyrazoline, 4*H*-pyran, chromanyl, imidazolidinyl, imidazolinyl, indolinyl, isochromanyl, isoindolinyl, morpholine, piperazinyl, piperidine, piperidyl, pyrazolidine, pyrazolidinyl, pyrazolinyl, pyrrolidine, pyrroline, quinuelidine, thiomorpholine, and the like.

The term "alkylene" refers to a divalent straight or branched hydrocarbon chain (*e.g.* ethylene $-CH_2CH_2-$).

The term "aryl(C_1-C_8)alkylene" for example includes benzyl, phenethyl, 3-phenylpropyl, naphthylmethyl and the like.

The terms "systemic intoxification" or "inflammatory shock" refer to the build-up of toxins or an intense inflammatory response in the body due to the invasion and/or treatment of bacteria, fungi or viruses.

As used herein "anti-pathogenic agent" refers to compounds that have anti-bacterial, anti-fungal or antiviral activity.

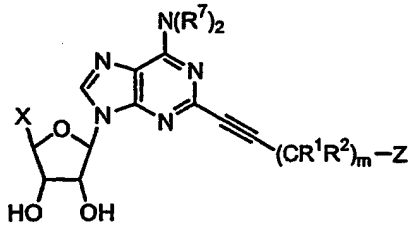
As used herein the term "in conjunction with" refers to co-administration of an antibacterial agent, an antifungal agent or an antiviral agent with the A_{2A} adenosine receptor agonist. The agents and the A_{2A} adenosine receptor agonists can be administered either simultaneously or as a mixture or they can be administered subsequently. The subsequent administration of the A_{2A} adenosine receptor agonists can be prior to the agent, within minutes or up to about 48 hours after the administration of the agent. Preferably the administration of the A_{2A} adenosine receptor agonists will be within about 24 hours and more preferably within about 12 hours.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of

carbon atoms in the moiety, *i.e.*, the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, (C_1-C_8)alkyl refers to alkyl of one to eight carbon atoms, inclusive.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (*e.g.*, "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" for room temperature).

In one embodiment, agonists of A_{2A} adenosine receptors that are useful in the practice of the present invention include compounds having the formula (I):



(I)

wherein

Z is $CR^3R^4R^5$ or NR^4R^5; each R^1 is independently hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle, hetrocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^bR^cNC(=O)O$-, $R^aOC(=O)N(R^b)$-, R^bR^cN-, $R^bR^cNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^bR^cNC(=O)N(R^b)$-, $R^bR^cNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $R^aS(=O)_2$-, $-N=NR^b$, or $-OPO_2R^a$;

each R^2 is independently hydrogen, halo, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, or heteroaryl(C_1-C_8)alkylene-; or

R^1 and R^2 and the atom to which they are attached is C=O, C=S or C=NR^d,

R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, mono-, bicyclic- or aromatic ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms optionally comprising 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl (-$S(O)_2$-) or amine (-NR^b-) in the ring;

wherein any ring comprising R^4 and R^5 is substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently halo, -OR^a, -SR^a, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle or hetrocycle (C_1-C_8)alkylene-, aryl, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^bR^cNC(=O)O$-, $R^aOC(=O)N(R^b)$-, R^bR^cN-, $R^bR^cNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^bR^cNC(=O)N(R^b)$-, $R^bR^cNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-, -SSR^a, $R^aS(=O)$-, -NNR^b,-OPO_2R^a, or two R^6 groups and the atom to which they are attached is C=O, C=S or; two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring;

R^3 is hydrogen, halo, -OR^a, -SR^a, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle, hetrocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, -CO_2R^a, $R^aC(=O)O$-, $R^aC(=O)$-, -OCO_2R^a, $R^bR^cNC(=O)O$-, $R^aOC(=O)N(R^b)$-, R^bR^cN-, $R^bR^cNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^bR^cNC(=O)N(R^b)$-, $R^bR^cNC(=S)N(R^b)$-, -OPO_3R^a, $R^aOC(=S)$-, $R^aC(=S)$-,

$-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-NNR^b$, $-OPO_2R^a$; or if the ring formed from CR^4R^5 is aryl or hetreroaryl or partially unsaturated then R^3 can be absent;

each R^7 is independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl or aryl(C_1-C_8)alkylene, heteroaryl, heteroaryl(C_1-C_8)alkylene-;

X is $-CH_2OR^a$, $-CO_2R^a$, $-OC(O)R^a$, $-CH_2OC(O)R^a$, $-C(O)NR^bR^b$, $-CH_2SR^a$, $-C(S)OR^a$, $-OC(S)R^a$, $-CH_2OC(S)R^a$ or $-C(S)NR^bR^c$ or $-CH_2N(R^b)(R^c)$;

wherein any of the alkyl, cycloalkyl, heterocycle, aryl, or heteroaryl, groups of R^1, R^2, R^3, R^6 and $R^7$is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle or hetrocycle(C_1-C_8)-alkylene-, aryl, aryloxy, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)-alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^bR^cNC(=O)O-$, $R^aOC(=O)N(R^b)-$, R^bR^cN-, $R^bR^cNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^bR^cNC(=O)N(R^b)-$, $R^bR^cNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)_p-$, $R^bR^cNS(O)_p-$, $N=NR^b$, and $-OPO_2R^a$;

wherein any (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_1-C_8)alkoxy, (C_1-C_8)alkanoyl, (C_1-C_8)alkylene, or heterocycle, is optionally partially unsaturated;

each R^a, R^b and R^c is independently hydrogen, (C_1-C_8)alkyl, or (C_1-C_8)alkyl substituted with 1-3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, amino acid, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; or R^b and R^c, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and R^d is hydrogen or (C_1-C_6)alkyl; m is 0 to about 8 and p is 0 to 2; or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention includes the use of compounds of formula (I) provided that when CR^4R^5 is a carbocyclic ring then at least one of R^1, R^2, or R^3 is a group other than hydrogen or at least one R^6 group is a group other than $-CH_2OH$, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)OCH_2-$ or $R^bR^cNC(=O)-$; and provided that m is at least 1 when Z is NR^4R^5.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A specific value for R^1 is hydrogen, -OH, $-CH_2OH$, -OMe, -OAc, $-NH_2$, -NHMe, $-NMe_2$ or -NHAc.

Another specific value for R^1 is hydrogen, -OH, -OMe, -OAc, $-NH_2$, -NHMe, $-NMe_2$ or -NHAc.

Another specific value for R^1 is hydrogen, -OH, -OMe, or $-NH_2$.

Another specific value for R^1 is hydrogen, -OH, or $-NH_2$.

A more specific value for R^1 is hydrogen or -OH.

A specific value for R^1, R^2 and the carbon atom to which they are attached is carbonyl (C=O).

A specific value for R^2 is hydrogen or (C_1-C_8)alkyl, cyclopropyl, cyclohexyl or benzyl.

Another specific value for R^2 is hydrogen, methyl, ethyl or propyl.

Another specific value for R^2 is hydrogen or methyl.

A more specific value for R^2 is hydrogen

A specific value for R^3 is hydrogen, OH, OMe, OAc, NH_2, NHMe, NMe_2 or NHAc.

Another specific value for R^3 is hydrogen, OH, OMe, or NH_2.

Another specific value for R^3 is hydrogen, OH, or NH_2.

A more specific value for R^3 is hydrogen or OH.

A specific value for the ring comprising R^4, R^5 and the atom to which they are connected is cyclopentane, cyclohexane, piperidine, dihydro-pyridine, tetrahydro-pyridine, pyridine, piperazine, decaline, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, imidazole, dihydro-imidazole, imidazolidine, pyrazole, dihydro-pyrazole, and. pyrazolidine.

A more specific value for the ring comprising R^4 and R^5 and the atom to which they are connected is, cyclohexane, piperidine or piperazine.

A specific value for R^6 is $(C_1$-$C_8)$alkyl, or substituted $(C_1$-$C_8)$alkyl, $-OR^a$, $-CO_2R^a$, $R^aC(=O)$-, $R^aC(=O)O$-, R^bR^cN-, $R^bR^cNC(=O)$-, or aryl.

Another specific value for R^6 is $(C_1$-$C_8)$alkyl, $-OR^a$, $-CO_2R^a$, $R^aC(=O)$-, $R^aC(=O)O$-, R^bR^cN-, $R^bR^cNC(=O)$-, or aryl.

Another specific value for R^6 is methyl, ethyl, butyl, OH, OR^a, $-CO_2R^a$, $R^aC(=O)$-, $OC(=O)CH_2CH_3$, $-CONR^bR^c$, $-NR^bR^c$ or phenyl.

Another specific value for R^6 is OH, OMe, methyl, ethyl, t-butyl, $-CO_2R^a$, $-C(=O)NR^bR^c$, -OAc, $-NH_2$, -NHMe, $-NMe_2$, -NHEt or $-N(Et)_2$.

Another specific value for R^6 is $-(CH_2)_{1-2}OR^a$, $-(CH_2)_{1-2}C(=O)OR^a$, $-(CH_2)_{1-2}OC(=O)R^a$, $-(CH_2)_{1-2}C(=O)R^a$, $-(CH_2)_{1-2}OCO_2R^a$, $-(CH_2)_{1-2}NHR^a$, $-(CH_2)_{1-2}NR^bR^c$, $-(CH_2)_{1-2}OC(=O)NHR^a$, or $-(CH_2)_{1-2}OC(=O)NR^bR^c$.

Another specific value for R^6 is $-CH_2OH$, $-CH_2OAc$, $-CH_2OCH_3$, $-CH_2C(=O)OCH_3$, $-CH_2OC(=O)CH_3$, $-CH_2C(=O)CH_3$, $-CH_2OCO_2CH_3$, $-CH_2NH(CH_3)$, or $-(CH_2)_{1-2}N(CH_3)_2$.

Another specific value for R^6 is methyl, ethyl, t-butyl, phenyl, $-CO_2R^a$, $-CONR^bR^c$, or $R^aC(=O)$-.

Another specific value for R^6 is $-CH_2OH$, $-CH_2OAc$, $-C(=O)OCH_3$, $-C(=O)CH_3$, OCO_2CH_3 $-OCO_2CH_3$, $-CH_2NH(CH_3)$, or $-(CH_2)_{1-2}N(CH_3)_2$.

A more specific value for R^6 is methyl, ethyl, $-CO_2R^a$ $-CONR^bR^c$, or $R^aC(=O)$-.

A specific number of R^6 groups substituted on the R^4R^5 ring is from1 to about 4.

Specific values for R^a and R^b are independently hydrogen, (C_1-C_4)alkyl, aryl or aryl(C_1-C_8)alkylene.

More specific values for R^a and R^b are independently hydrogen, methyl, ethyl, phenyl or benzyl.

A more specific value for R^a is (C_1-C_8)alkyl.

Another specific value for R^a is methyl, ethyl, propyl or butyl.

A more specific value for R^a is methyl, ethyl, i-propyl, i-butyl or *tert*-butyl.

Another specific value for R^b and R^c is a ring

A specific value for R^7 is hydrogen, alkyl, aryl or aryl(C_1-C_8)alkylene.

Another specific value for R^7 is hydrogen, methyl or ethyl, phenyl or benzyl.

A more specific value for R^7 is H, or methyl.

A specific value for $-N(R^7)_2$ is amino, methylamino, dimethylamino, ethylamino, pentylamino, diphenylethylamino, pyridylmethylamino, diethylamino or benzylamino.

A specific value for $-N(R^7)_2$ is amino, methylamino, dimethylamino, ethylamino, diethylamino diphenylethylamino, pentylamino or benzylamino.

A specific value for $N(R^7)_2$ is amino, or methylamino.

A specific value for X is $-CH_2OR^a$, $-CO_2R^a$, $-OC(O)R^a$, $-CH_2OC(O)R^a$, $-C(O)NR^bR^c$.

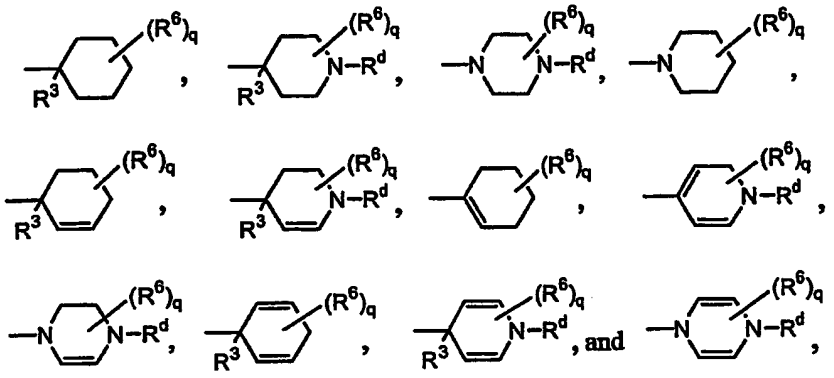
Another specific value for X is $-CH_2OR^a$ or $-C(O)NR^bR^c$.

A more specific value for X is $-CH_2OH$ or $-C(O)NHCH_2CH_3$.

A specific value for m is 0, 1, or 2.

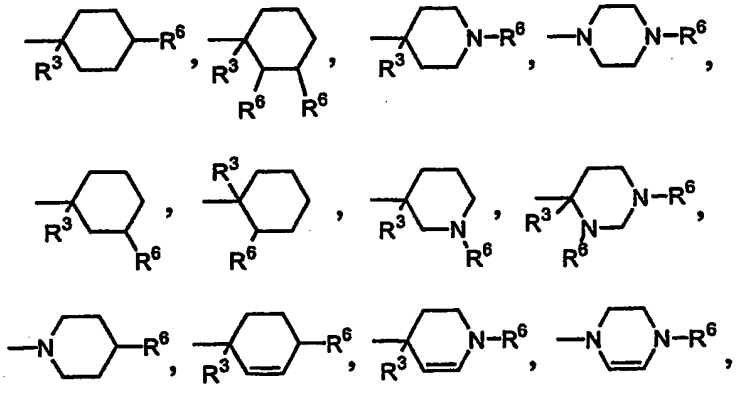
A more specific value for m is 0, or 1.

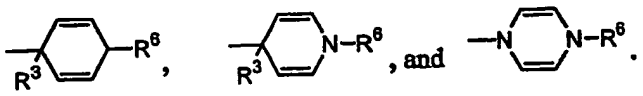
Specific examples of rings comprising R^4, R^5 and the atom to which they are connected include:



where q is from 0 to 14 and R^d is hydrogen, provided that when q is zero then R^d is not hydrogen.

More specific examples of rings comprising R^4, R^5 and the atom to which they are connected include:





Specific values for the ring comprising R^4, R^5 and the atom to which they are connected are 2-methyl cyclohexane, 2,2-dimethylcyclohexane, 2-phenylcyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butyl cyclohexane, 3-methyl cyclohexane, 3,3-dimethylcyclohexane, 4-methyl cyclohexane, 4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butyl cyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane. 4-cyclohexanecarboxyic acid, 4-cyclohexanecarboxyic acid esters, or 4-methyloxyalkanoyl-cyclohexane.

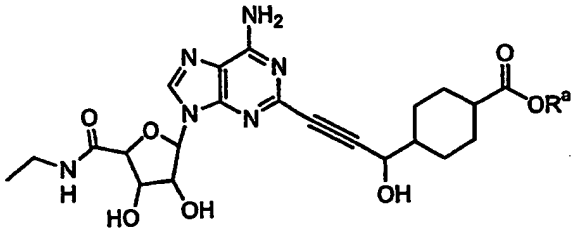
More specific values for the ring comprising R^4, R^5 and the atom to which they are connected are 4-piperidine, 4-piperidene-1-carboxylic acid, 4-piperidine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid ethyl ester, 4-piperidine-1-carboxylic acid propyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester, 1-piperidine, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-carboxylic acid ethyl ester, 1-piperidine-4-carboxylic acid propyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester, 1-piperidine-4-carboxylic acid methyl ester, 3-piperidine, 3-piperidene-1-carboxylic acid, 3-piperidine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butyl ester, 1,4-piperazine, 4-piperazine-1-carboxylic acid, 4-piperazine-1-carboxylic acid methyl ester, 4-piperazine-1-carboxylic acid ethyl ester, 4-piperazine-1-carboxylic acid propyl ester, 4-piperazine-1-carboxylic acid tert-butylester, 1,3-piperazine, 3-piperazine-1-carboxylic acid, 3-piperazine-1-carboxylic acid methyl ester, 3-piperazine-1-carboxylic acid ethyl ester, 3-piperazine-1-carboxylic acid propyl ester, 3-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-3-carboxylic acid methyl ester,

1-piperidine-3-carboxylic acid ethyl ester, 1-piperidine-3-carboxylic acid propyl ester or 1-piperidine-3-caboxylic acid tert-butyl ester.

Another group of specific values for the ring comprising R^4 and R^5 are 2-methyl cyclohexane, 2,2-dimethylcyclohexane, 2-phenyl cyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butyl cyclohexane, 3-methyl cyclohexane, 3,3-dimethylcyclohexane, 4-methyl cyclohexane, 4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butyl cyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane, 4-piperidine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester 4-piperidine, 4-piperazine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester, tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, or 1-piperidine-4-caboxylic acid tert-butyl ester, 3-piperidine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butyl ester, 3-piperidine, 3-piperazine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid *tert*-butylester, 1-piperidine-3-carboxylic acid methyl ester, 1-piperidine-3-caboxylic acid *tert*-butyl ester

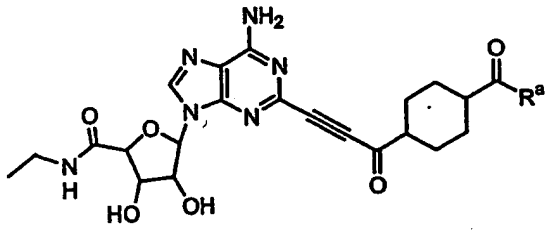
Specific compounds of formula (I) are those wherein each R^7 is H, X is ethylaminocarbonyl and

R^1 is hydroxy, R^2 is hydrogen, and Z is 4-carboxycyclohexyl, wherein R^a is hydrogen, 4; Z is 4-methoxycarbonylcyclohexylmethyl, R^a is methyl, 5; R^1 and R^2 together are oxo, Z is a 4-carbonylcyclohexyl group, wherein R^a is methyl, methoxy, ethyl, ethoxy, propyl, isopropoxy, -isobutyl, *tert*-butyl, amine, methylamine or dimethylamine, 6.



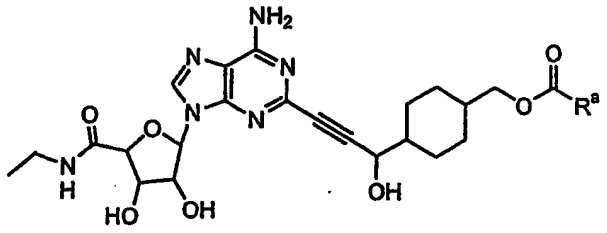
4, R^a is H

5, R^a is CH_3



6

Another group of specific compounds of formula (I) are those wherein each R^7 is H, X is ethylaminocarbonyl, R^1 is hydroxy, R^2 is hydrogen, and Z is a substituted 4-(methyleneoxycarbonyl)cyclohexyl group, wherein R^a is methyl, ethyl, propyl, *tert*-butyl, methoxy, ethoxy, methylamine or dimethylamine, 7; or R^1 and R^2 together are oxo, and Z is a substituted -(methyleneoxycarbonyl)cyclohexyl group, wherein R^a is methyl, ethyl, propyl, *tert*-butyl, methoxy, ethoxy, methylamine or dimethylamine, 8.



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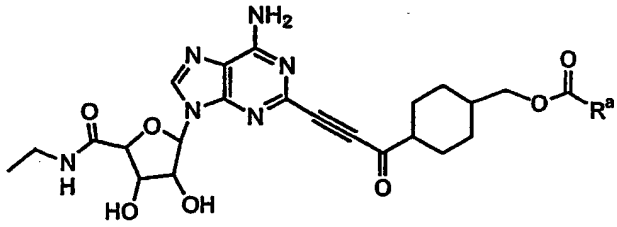
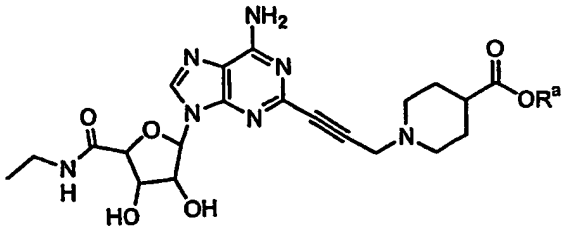


8

Another group of specific compounds of formula (I) are those wherein each R^7 is H, X is ethylaminocarbonyl, and R^1 and R^2 are each hydrogen, and Z is a 1-piperidyl-4-carboxylic acid or ester group, wherein R^a is hydrogen, methyl, ethyl, propyl, isopropyl, or t-butyl, 9; R^1 and R^2 together are oxo, and Z is a 1-piperidyl-4-carboxylic acid or ester group, wherein R^a is hydrogen, methyl, ethyl, propyl, isopropyl, or t-butyl, 10; R^1 and R^2 are each hydrogen and Z is a 4-(methyleneoxycarbonyl)piperidin-4-yl group wherein R^a is methyl, ethyl, propyl or t-butyl, amine, methylamine, dimethylamine, 11; or R^1 and R^2 together are oxo, and Z is a 4-(methyleneoxycarbonyl)piperidin-4-yl wherein R^a is methyl, ethyl, propyl or t-butyl, amine, methylamine, dimethylamine, 12; R^1 and R^2 are each hydrogen and Z is a 4-(methyleneoxy-carbonyl)piperidin-4-yl-oxy wherein R^a is hydrogen, methyl, ethyl, propyl isopropyl, isobutyl, or t-butyl, 13or R^1 and R^2 together are oxo, Z is a

4-(methyleneoxycarbonyl)piperidin-4-yl-oxy wherein R^a is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, or t-butyl, 14.



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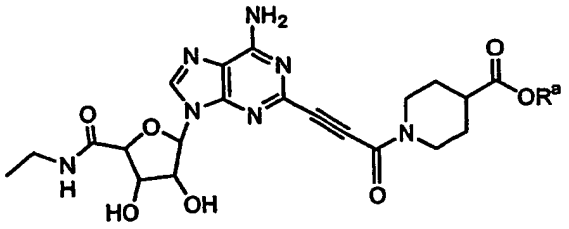

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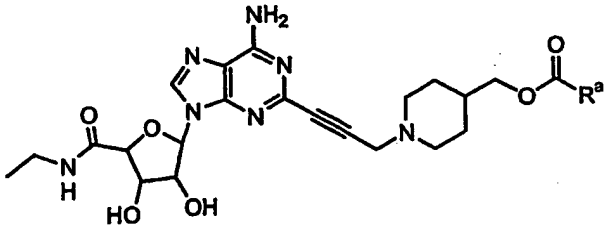

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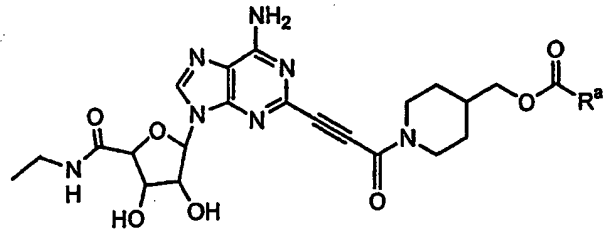

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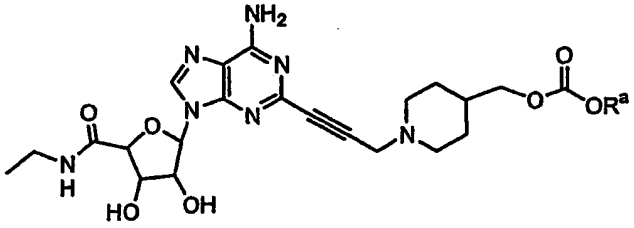

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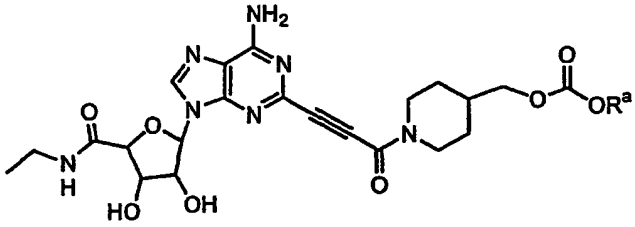
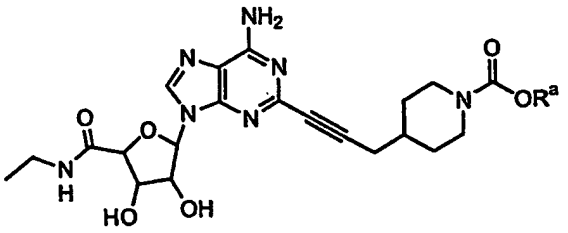


14

Another group of specific compounds of formula (I) are those wherein each R^7 is H, X is ethylaminocarbonyl, R^1 and R^2 are each hydrogen, and Z is a 4-piperidyl-1-carboxylic acid or ester group, wherein R^a is methyl, ethyl, propyl, isopropyl, isobutyl, or t-butyl, 15, R^1 is hydroxy, R^2 is hydrogen, and Z is a 4-piperidyl-1-carboxylic acid or ester group, wherein R^a is methyl,

ethyl, propyl, isopropyl, isobutyl, or t-butyl, **16**; or R^1 and R^2 together are oxo, and Z is a 4-piperidyl-1-carboxylic acid or ester group, wherein R^a is methyl, ethyl, propyl, isopropyl, isobutyl, or t-butyl, **17**.



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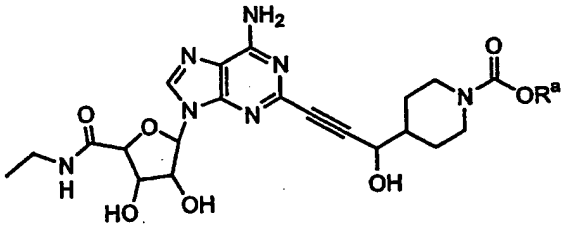

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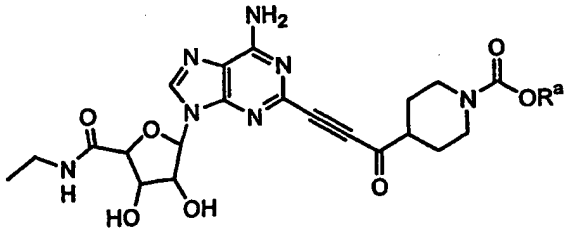
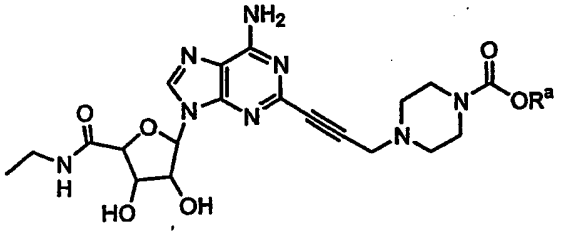
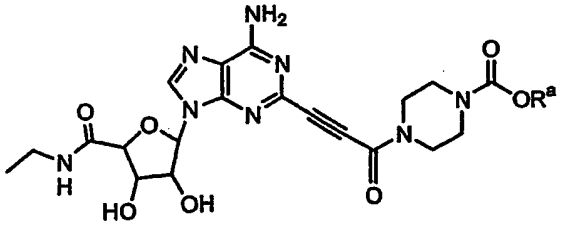


17

Another group of specific compounds of formula (I) are those wherein each R^7 is H, X is ethylaminocarbonyl, R^1 and R^2 are each hydrogen, Z is a 4-piperazine-1-carboxylic acid or ester group wherein R^a is methyl, ethyl, isopropyl, isobutyl, or t-butyl, **18**; or R^1 and R^2 together are oxo, Z is a 4-piperazine-1-carboxylic acid or ester group wherein R^a is methyl, ethyl, isopropyl, isobutyl, or t-butyl, **19**.



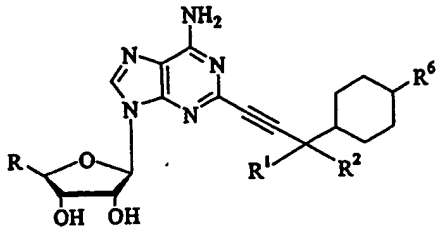
18



19

Additional compounds useful to practice the invention are depicted in tables 1, 2, 3, 4, 5, 6 and 7 below:

Table 1

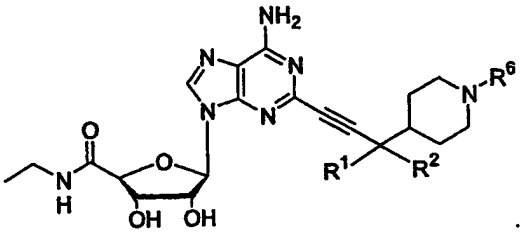


Compound	R	R^1	R^2	R^6
ATL2037	NECA	H	H	CH_2OH
MP9056	NECA	OH	H	CH_2OH
ATL146a	NECA	H	H	CO_2H
MP9057	NECA	OH	H	CO_2H
ATL146e	NECA	H	H	CO_2Me
MP9058	NECA	OH	H	CO_2Me
JR2145	CH_2OH	H	H	CO_2Me
MP9059	CH_2OH	OH	H	CO_2Me
ATL193	NECA	H	H	CH_2OAc
MP9060	NECA	OH	H	CH_2Oac
JR2147	CH_2OH	H	H	CH_2Oac
MP9061	CH_2OH	OH	H	CH_2Oac
JR3023	NECA	H	H	$CH_2N(CH_3)_2$
MP9062	NECA	OH	H	$CH_2N(CH_3)_2$
JR3021	NECA	H	H	$COOCH_2CH_2NHBoc$
MP9063	NECA	OH	H	$COOCH_2CH_2NHBoc$
JR3033	NECA	H	H	$COOCH_2CH_2NH_2$
MP9064	NECA	OH	H	$COOCH_2CH_2NH_2$

JR3037	NECA	H	H	$CONHCH_2CH_3$
MP9065	NECA	OH	H	$CONHCH_2CH_3$
JR3055	NECA	H	H	$CONH_2$
MP9072	NECA	OH	H	$CONH_2$
JR3065	NECA	H	H	CONHMe
MP9066	NECA	OH	H	CONHMe
JR3067B	NECA	H	H	Me, cis CO_2Me
MP9067	NECA	OH	H	Me, cis CO_2Me
JR3067A	NECA	H	H	Me, trans CO_2Me
MP9068	NECA	OH	H	Me, trans CO_2Me
JR3087	NECA	H	H	CH_2CH_3
MP9069	NECA	OH	H	CH_2CH_3
JR3159A	NECA	OH	H	H
JR3159B	NECA	OH	H	H
JR3119	NECA	H	H	$COCH_3$
MP9070	NECA	OH	H	$COCH_3$
JR3121	NECA	H	H	$CHCH_3(OH)$
MP9071	NECA	OH	H	$CHCH_3(OH)$
JR3139	NECA	OH	C_6H_{11}	H

NECA = $CH_3CH_2N(H)C(O)$-

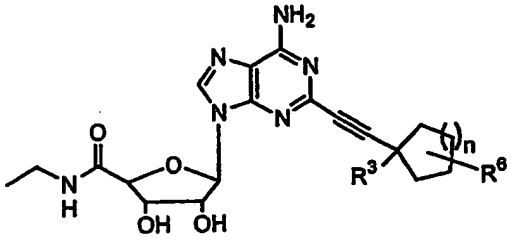
Table 2



Compound	R^1	R^2	R^6
JR3261	H	H	H
JR3259	H	H	CO_2tBu
JR3269	H	H	CO_2Et
JR4011	H	H	CO_2iBu
JR4009	H	H	CO_2iPr
JR4007	H	H	COMe
JR4051	H	H	$COC(CH_3)_3$
JR4047	H	H	$COCH_2(CH_3)_3$
MP9047	H	H	$COCH_3$
MP9048	H	H	$C(O)N(CH_3)_2$
MP9049	H	H	$C(O)N(CH_3)Et$
MP9050	H	H	$C(O)N(CH_3)iPr$
MP9051	H	H	$C(O)N(CH_3)iBu$
MP9052	H	H	$C(O)NH(CH_3)$
MP9053	H	H	C(O)NH(Et)
MP9054	H	H	C(O)NH(iPr)
MP9055	H	H	C(O)NH(iBu)
TX3261	OH	H	H
TX3259	OH	H	CO_2tBu
TX3269	OH	H	CO_2Et
TX4011	OH	H	CO_2iBu
TX4009	OH	H	CO_2iPr
TX4007	OH	H	COMe

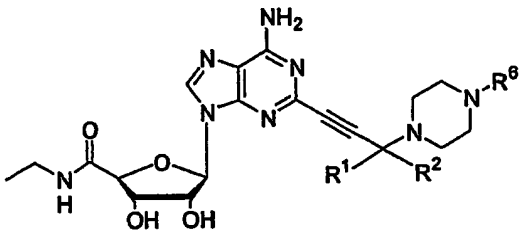
TX4051	OH	H	$COC(CH_3)_3$
TX4047	OH	H	$COCH_2(CH_3)_3$
TX9047	OH	H	$COCH_3$
TX9048	OH	H	$C(O)N(CH_3)_2$
TX9049	OH	H	$C(O)N(CH_3)Et$
TX9050	OH	H	$C(O)N(CH_3)iPr$
TX9051	OH	H	$C(O)N(CH_3)iBu$
TX9052	OH	H	$C(O)NH(CH_3)$
TX9053	OH	H	C(O)NH(Et)
TX9054	OH	H	C(O)NH(iPr)
TX9055	OH	H	C(O)NH(iBu)

Table 3



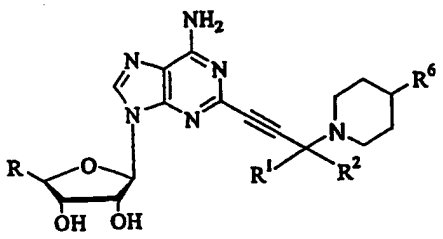
Compound	n	R^3	R^6
JR3135	1	OH	H
JR3089	2	OH	H
JR3205	2	NH_2	H
JR3177A	2	OH	2-CH_3
JR3177B	2	OH	2-CH_3
JR3181A	2	OH	2-CH_3
JR3181B	2	OH	2-CH_3
JR3227	2	OH	2-$C(CH_3)_3$
JR9876	2	OH	2-C_6H_5
JR3179	2	OH	3-CH_3
JR3221	2	OH (R)	3-CH_3 (R)
ATL 203	2	OH (S)	3-CH_3 (R)
MP9041	2	OH (R)	3-CH_3 (S)
MP9042	2	OH (S)	3-CH_3 (S)
JR3201B	2	OH	3-$(CH_3)_2$
MP9043	2	OH (R)	3-CH_2CH_3 (R)
MP9044	2	OH (S)	3-CH_2CH_3 (R)
MP9045	2	OH (R)	3-CH_2CH_3 (S)
MP9046	2	OH (S)	3-CH_2CH_3 (S)
JR3163	2	OH	3-$(CH_3)_2$, 5-$(CH_3)_2$
JR9875	2	OH	4-CH_3
JR3149	2	OH	4-C_2H_5
JR3203	2	OH	4-$C(CH_3)_3$
JR3161	2	OH	4-C_6H_5

Table 4



Compound	R^1	R^2	R^6
JR3213	H	H	CO_2Et
JR3281	H	H	CO_2tBu
JR3289	H	H	H
JR4025	H	H	cyclohexyl
JR4053	H	H	COMe
JR4049	H	H	CO_2iBu
JR3283	H	H	2-Pyrimidinyl
MP9029	H	H	COMe
MP9030	H	H	$COC(CH_3)_3$
MP9031	H	H	$COCH_2(CH_3)_3$
MP9032	H	H	$COCH_3$
MP9033	H	H	$C(O)N(CH_3)_2$
MP9034	H	H	$C(O)N(CH_3)Et$
MP9035	H	H	$C(O)N(CH_3)iPr$
MP9036	H	H	$C(O)N(CH_3)iBu$
MP9037	H	H	$C(O)NH(CH_3)$
MP9038	H	H	C(O)NH(Et)
MP9039	H	H	C(O)NH(iPr)
MP9040	H	H	C(O)NH(iBu)

Table 5

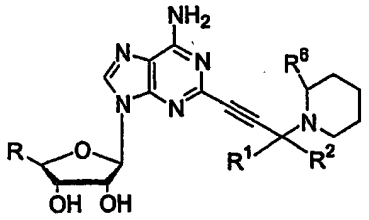


Compound	R	R^1	R^2	R^6
MP9021	NECA	H	H	CH_2OH
MP9022	NECA	H	H	CO_2H
JR3251	NECA	H	H	CO_2Me
JR3279	NECA	H	H	CO_2Et
MP9027	CH_2OH	H	H	CO_2Me
MP9028	NECA	H	H	CO_2MeCH_2OAc
MP9015	CH_2OH	H	H	CH_2OAc
MP9016	NECA	H	H	$CH_2N(CH_3)_2$
MP9017	NECA	H	H	$COOCH_2CH_2NHBoc$
MP9018	NECA	H	H	$COOCH_2CH_2NH_2$
MP9019	NECA	H	H	$CONHCH_2CH_3$
MP9020	NECA	H	H	$CONH_2$
MP9023	NECA	H	H	CONHMe
MP9024	NECA	H	H	CH_2CH_3
MP9025	NECA	H	H	$COCH_3$
MP9026	NECA	H	H	$CHCH_3(OH)$

NECA = $CH_3CH_2N(H)C(O)$-

5

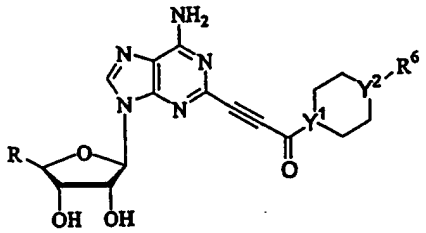
Table 6



Compound	R	R^1	R^2	R^6
MP9001	NECA	H	H	CH_2OH
MP9002	NECA	H	H	CO_2H
JR3253	NECA	H	H	CO_2Me
MP9003	CH_2OH	H	H	CO_2Me
MP9004	NECA	H	H	CH_2OAc
MP9005	CH_2OH	H	H	CH_2OAc
MP9006	NECA	H	H	$CH_2N(CH_3)_2$
MP9007	NECA	H	H	$COOCH_2CH_2NHBoc$
MP9008	NECA	H	H	$COOCH_2CH_2NH_2$
MP9009	NECA	H	H	$CONHCH_2CH_3$
MP9010	NECA	H	H	$CONH_2$
MP9011	NECA	H	H	CONHMe
MP9012	NECA	H	H	CH_2CH_3
MP9013	NECA	H	H	$COCH_3$
MP9014	NECA	H	H	$CHCH_3(OH)$

NECA = $CH_3CH_2N(H)C(O)$-

Table 7



Compound	R	Y	Y'	R6
RJ1111	NECA	CH	CH	CO_2Me
RJ1112	NECA	CH	N	CO_2Me
RJ1113	NECA	N	CH	CO_2Me
RJ1114	NECA	N	N	CO_2Me
RJ1115	NECA	CH	CH	CH_2OH
RJ1116	NECA	CH	N	CH_2OH
RJ1117	NECA	N	CH	CH_2OH
RJ1118	NECA	N	N	CH_2OH
RJ1119	NECA	CH	CH	CO_2H
RJ1120	NECA	CH	N	CO_2H
RJ1121	NECA	N	CH	CO_2H
RJ1122	NECA	N	N	CO_2H
RJ1123	NECA	CH	CH	CH_2OAc
RJ1124	NECA	CH	N	CH_2OAc
RJ1125	NECA	N	CH	CH_2OAc
RJ1126	NECA	N	N	CH_2OAc
RJ1127	NECA	CH	CH	$CONH_2$
RJ1128	NECA	CH	N	$CONH_2$
RJ1129	NECA	N	CH	$CONH_2$
RJ1130	NECA	N	N	$CONH_2$
RJ1131	NECA	CH	CH	CONHMe
RJ1132	NECA	CH	N	CONHMe
RJ1133	NECA	N	CH	CONHMe
RJ1134	NECA	N	N	CONHMe
RJ1135	NECA	CH	CH	CO_2tBu
RJ1136	NECA	CH	N	CO_2tBu
RJ1137	NECA	N	CH	CO_2tBu
RJ1138	NECA	N	N	CO_2tBu
RJ1139	NECA	CH	CH	CO_2Et

RJ1140	NECA	CH	N	CO_2Et
RJ1141	NECA	N	CH	CO_2Et
RJ1142	NECA	N	N	CO_2Et
RJ1143	NECA	CH	CH	CO_2iBu
RJ1144	NECA	CH	N	CO_2iBu
RJ1145	NECA	N	CH	CO_2iBu
RJ1146	NECA	N	N	CO_2iBu
RJ1147	NECA	CH	CH	CO_2iPr
RJ1148	NECA	CH	N	CO_2iPr
RJ1149	NECA	N	CH	CO_2iPr
RJ1150	NECA	N	N	CO_2iPr
RJ1151	NECA	CH	CH	COMe
RJ1152	NECA	CH	N	COMe
RJ1153	NECA	N	CH	COMe
RJ1154	NECA	N	N	COMe
RJ1155	NECA	CH	CH	$COC(CH_3)_3$
RJ1156	NECA	CH	N	$COC(CH_3)_3$
RJ1157	NECA	N	CH	$COC(CH_3)_3$
RJ1158	NECA	N	N	$COC(CH_3)_3$
RJ1159	NECA	CH	CH	$COCH_2(CH_3)_3$
RJ1160	NECA	CH	N	$COCH_2(CH_3)_3$
RJ1161	NECA	N	CH	$COCH_2(CH_3)_3$
RJ1162	NECA	N	N	$COCH_2(CH_3)_3$
RJ1163	NECA	CH	CH	$C(O)N(CH_3)_2$
RJ1164	NECA	CH	N	$C(O)N(CH_3)_2$
RJ1165	NECA	N	CH	$C(O)N(CH_3)_2$
RJ1166	NECA	N	N	$C(O)N(CH_3)_2$
RJ1167	NECA	CH	CH	$C(O)N(CH_3)Et$
RJ1168	NECA	CH	N	$C(O)N(CH_3)Et$
RJ1169	NECA	N	CH	$C(O)N(CH_3)Et$
RJ1170	NECA	N	N	$C(O)N(CH_3)Et$
RJ1171	NECA	CH	CH	$C(O)N(CH_3)iPr$
RJ1172	NECA	CH	N	$C(O)N(CH_3)iPr$
RJ1173	NECA	N	CH	$C(O)N(CH_3)iPr$
RJ1174	NECA	N	N	$C(O)N(CH_3)iPr$
RJ1175	NECA	CH	CH	$C(O)N(CH_3)iBu$
RJ1176	NECA	CH	N	$C(O)N(CH_3)iBu$
RJ1177	NECA	N	CH	$C(O)N(CH_3)iBu$
RJ1178	NECA	N	N	$C(O)N(CH_3)iBu$

RJ1179	NECA	CH	CH	C(O)NH(Et)
RJ1180	NECA	CH	N	C(O)NH(Et)
RJ1181	NECA	N	CH	C(O)NH(Et)
RJ1182	NECA	N	N	C(O)NH(Et)
RJ1183	NECA	CH	CH	C(O)NH(iPr)
RJ1184	NECA	CH	N	C(O)NH(iPr)
RJ1185	NECA	N	CH	C(O)NH(iPr)
RJ1186	NECA	N	N	C(O)NH(iPr)
RJ1187	NECA	CH	CH	C(O)NH(iBu)
RJ1188	NECA	CH	N	C(O)NH(iBu)
RJ1189	NECA	N	CH	C(O)NH(iBu)
RJ1190	NECA	N	N	C(O)NH(iBu)
RJ1191	NECA	CH	CH	CH_2OCOCH_3
RJ1192	NECA	N	CH	CH_2OCOCH_3
RJ1193	NECA	CH	CH	CH_2OCOEt
RJ1194	NECA	N	CH	CH_2OCOEt
RJ1195	NECA	CH	CH	$CH_2OCOiPr$
RJ1196	NECA	N	CH	$CH_2OCOiPr$
RJ1197	NECA	CH	CH	$CH_2OCOiBu$
RJ1198	NECA	N	CH	$CH_2OCOiBu$

NECA = $CH_3CH_2N(H)C(O)$-

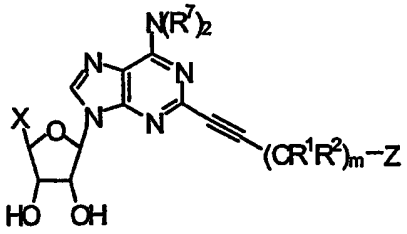
Examples of anti-bacterial agents suitable for use in the present invention include, but are not limited to, acediasulfone, acetosulfone, amikacin, amoxicillin, amphotericin B, ampicillin, apramycin, arbekacin, aspoxicillin, aztreonam, brodimoprim, butirosin, capreomycin, carumonam, cefadroxil, cefatrizine, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefminox, cefodizime, ceforanide, cefotaxime, cefotiam, cefozopran, cefpirome, cefprozil, cefroxadine, ceftazidime, cefteram, ceftibuten, ceftriaxone, cefuzonam, cephalexin, cephaloglycin, cephalosporin C, cephradine, ciprofloxacin, clinafloxacin, colistin, cyclacillin, dapsone, diathymosulfone, dibekacinm, enviomycinm, epicillin, fortimicin(s), gentamicin(s), gramicidin S, isepamicin, kanamycin(s), lucensomycin, lymecycline, micronomicin, natamycin, neomycin, netilmicin, paromomycin, pazufloxacin, penicillin N, peplomycin, perimycin A, polymyxin, p-sulfanilylbenzylamine, ribostamycin, ristocetin, sisomicin,

sparfloxacin, succisulfone, 2-p-sulfanilylanilinoethanol, 4,4'-sulfinyldianiline, sulfachrysoidine, sulfamidochrysoidine, sulfanilic acid, sulfoxone, teicoplanin, tetroxoprim, thiazolsulfone, tigemonam, tobramycin, tosufloxacin, trimethoprim, trovafloxacin, tuberactinomycin, vancomycin and the like. Preferred antibiotic agents are ciprofloxacin and ceftriaxone.

Examples of anti-fungal (anti-yeast) agents suitable for use in the present invention include, but are not limited to amphotericin B, azaserine, candicidin(s), lucensomycin, mepartricin, natamycin, nystatin, tubercidin and the like.

Examples of antiviral agents suitable for use in the present invention include, but are not limited to abacavir, acyclovir, amantadine, famciclovir, foscavir, ganciclovir, indinavir, lamivudine, lopinavir, ritonavir and the like.

In another embodiment, agonists of A_{2A} adenosine receptors that are useful in the practice of the present invention include compounds having the formula (II):



(II)

wherein Z is $CR^3R^4R^5$; each R^1, R^2 and R^3 is hydrogen; R^4 and R^5 together with the carbon atom to which they are attached form a cycloalkyl ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms; and

wherein the ring comprising R^4 and R^5 is substituted with $-(CH_2)_{0-6}$-Y; where Y is $-CH_2OR^a$, $-CO_2R^a$, $-OC(O)R^a$, $-CH_2OC(O)R^a$, $-C(O)NR^bR^c$, $-CH_2SR^a$, $-C(S)OR^a$, $-OC(S)R^a$, $-CH_2OC(S)R^a$ or $C(S)NR^bR^c$ or $-CH_2N(R^b)(R^c)$;

each R^7 is independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl or aryl(C_1-C_8)alkylene;

X is $-CH_2OR^a$, $-CO_2R^a$, $-OC(O)R^a$, $-CH_2OC(O)R^a$, $-C(O)NR^bR^c$, $-CH_2SR^a$, $-C(S)OR^a$, $-OC(S)R^a$, $-CH_2OC(S)R^a$ or $C(S)NR^bR^c$ or $-CH_2N(R^b)(R^c)$;

each R^a, R^b and R^c is independently hydrogen, (C_1-C_8)alkyl, or (C_1-C_8)alkyl substituted with 1-3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, amino acid, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; or R^b and R^c, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and m is 0 to about 6; or a pharmaceutically acceptable salt thereof.

A specific value for $-N(R^7)_2$ is amino, monomethylamino or cyclopropylamino.

A specific value for Z is carboxy- or -(C_1-C_4)alkoxycarbonyl-cyclohexyl(C_1-C_4)alkyl.

A specific value for R^a is H or (C_1-C_4)alkyl, i.e., methyl or ethyl.

A specific value for R^b is H, methyl or phenyl.

A specific value for R^c is H, methyl or phenyl.

A specific value for $-(CR^1R^2)_m-$ is $-CH_2-$ or $-CH_2-CH_2-$.

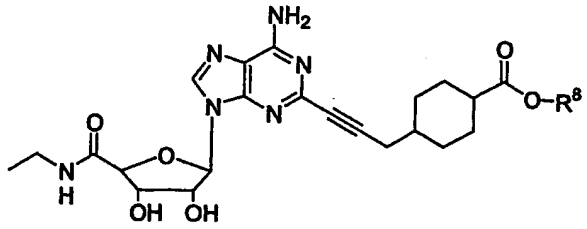
A specific value for X is CO_2R^a, (C_2-C_5)alkanoylmethyl or amido.

A specific value for Y is CO_2R^a, (C_2-C_5)alkanoylmethyl or amido.

A specific value for m is 1.

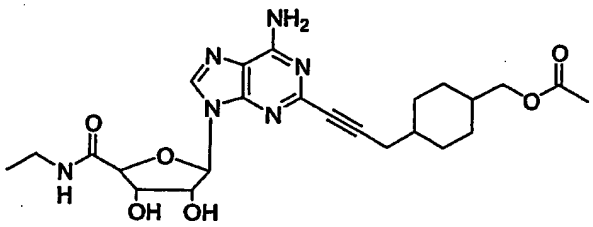
Specific A_{2A} adenosine receptor agonists suitable for use with the present invention having formula (II) include those described in US Patent No: 6,232,297. Preferred compounds of formula (II) are those wherein each R^7 is H, X is ethylaminocarbonyl and Z is 4-carboxycyclohexylmethyl (DWH-146a), Z is 4-

methoxycarbonylcyclohexylmethyl (DWH-146e), Z is 4-isopropylcarbonyl-cyclohexylmethyl (AB-1), Z is 4-acetoxymethyl-cyclohexylmethyl (JMR-193) or Z is 4-pyrrolidine-1-carbonylcyclohexylmethyl (AB-3). These comounds are depicted below.

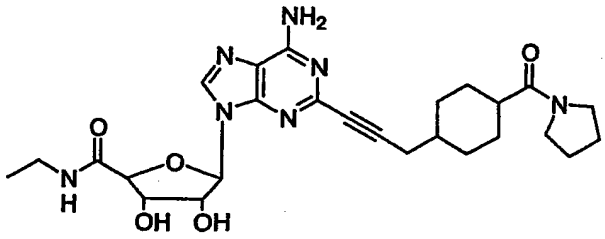


DWH-146: R^8 = H or Me.

AB-1: R^8 = iPr



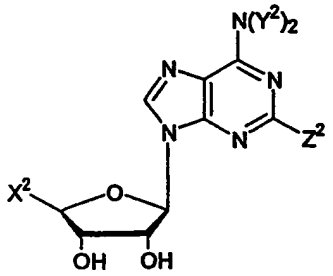
JMR-193



AB-3

The specific A_{2A} adenosine receptor agonists suitable for use with the present invention having formula (II) include those described in U.S. Patent No. 6, 232,297. These compounds, having formula (II), can be prepared according to the methods described therein.

Another specific group of agonists of A_{2A} adenosine receptors that are useful in the practice of the present invention include compounds having the general formula (III):



(III)

wherein Z^2 is a group selected from the group consisting of $-OR^{12}$, $-NR^{13}R^{14}$, a $-C{\equiv}C-Z^3$, and $-NH-N{=}R^{17}$;

each Y^2 is individually H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl or phenyl C_1-C_3 alkyl;

R^{12} is

a) C_{1-4} -alkyl;

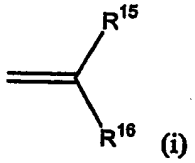
b) C_{1-4}-alkyl substituted with one or more C_{1-4} -alkoxy groups, halogens (fluorine, chlorine or bromine), hydroxy groups, amino groups, mono(C_{1-4} -alkyl)amino groups, di(C_{1-4}-alkyl)amino groups or C_{6-10}-aryl groups wherein the aryl groups may be substituted with one or more halogens (fluorine, chlorine or bromine), C_{1-4}-alkyl groups, hydroxy groups, amino groups, mono(C_{1-4}-alkyl)amino groups or di(C_{1-4}-alkyl)amino groups); or

c) C_{6-10}-aryl; or (d) C_{6-10}-aryl substituted with one or more halogens (fluorine, chlorine or bromine), hydroxy groups,

amino groups, mono(C_{1-4}-alkyl)amino groups, di(C_{1-4}-alkyl)amino groups or C_{1-4}-alkyl groups;

one of R^{13} and R^{14} has the same meaning as R^{12} and the other is hydrogen; and

R^{17} is a group having the formula (i)



(i)

wherein each of R^{15} and R^{16} independently may be hydrogen, (C_3-C_7)cycloalkyl or any of the meanings of R^{12}, provided that R^{15} and R^{16} are not both hydrogen;

X^2 is CH_2OH, CH_3, CO_2R^{20} or $C(=O)NR^{21}R^{22}$ wherein R^{20} has the same meaning as R^{13} and wherein R^{21} and R^{22} have the same meanings as R^{15} and R^{16} or R^{21} and R^{22} are both H;

Z^3 has one of the following meanings:

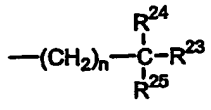
a) C_6-C_{10} aryl, optionally substituted with one to three halogen atoms, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_6 alkoxycarbonyl, C_2-C_6 alkoxyalkyl, C_1-C_6 alkylthio, thio, CHO, cyanomethyl, nitro, cyano, hydroxy, carboxy, C_2-C_6 acyl, amino C_1-C_3 monoalkylamino, C_2-C_6 dialkylamino, methylenedioxy or aminocarbonyl;

b) a group of formula $-(CH_2)_q$–Het wherein q is 0 or an integer from 1 to 3 and Het is 5 or 6 membered heterocyclic aromatic or non-aromatic ring, optionally benzocondensed, containing 1 to 3 heteroatoms selected from nonperoxide oxygen,

nitrogen or sulphur, linked through a carbon atom or through a nitrogen atom;

c) C_3-C_7 cycloalkyl optionally containing unsaturation or C_2-C_4 alkenyl;

d)



(ii)

wherein

R^{23} is hydrogen, methyl or phenyl;

R^{24} is hydrogen, C_1-C_6 linear or branched alkyl, C_5-C_6 cycloalkyl or C_3-C_7 cycloalkenyl, phenyl-C_1-C_2-alkyl or R^{23} and R^{24}, taken together, form a 5 or 6-membered carbocyclic ring or R^{25} is hydrogen and R^{23} and R^{24}, taken together, form an oxo group or a corresponding acetalic derivative;

R^{25} is OH, NH_2 dialkylamino, halogen, cyano; and n is 0 or 1 to 4; or

e) C_1-C_{16} alkyl, optionally comprising 1-2 double bonds, O, S or NY^2;

or a pharmaceutically acceptable salt thereof.

Specific C_{6-10}-aryl groups include phenyl and naphthyl.

Preferably, in the compound of formula (I), Z^2 is a group of the formula (iii)

$$-O-(CH_2)_n-Ar \qquad \text{(iii)}$$

wherein n is an integer from 1-4, preferably 2, and Ar is a phenyl group, tolyl group, naphthyl group, xylyl group or mesityl group. Most preferably Ar is a para-tolyl group and n = 2.

Preferably, in the compound of formula (II), Z^2 is a group of the formula (iv)

$$-NH-N=CHCy \qquad (iv)$$

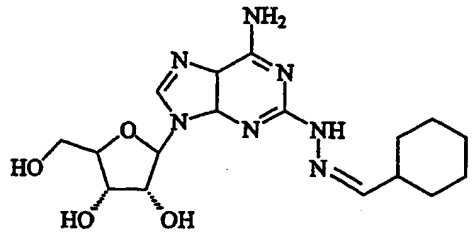
wherein Cy is a C_{3-7}-cycloalkyl group, preferably cyclohexyl or a C_{1-4} alkyl group, preferably isopropyl.

Preferably, in the compound of formula (II), Z^2 is a group of the formula (vii)

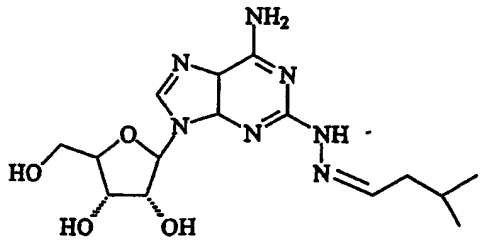
$$-C\equiv C-Z^3 \qquad (v)$$

wherein Z^3 is C_3-C_{16} alkyl, hydroxy C_2-C_6 alkyl or (phenyl) (hydroxymethyl).

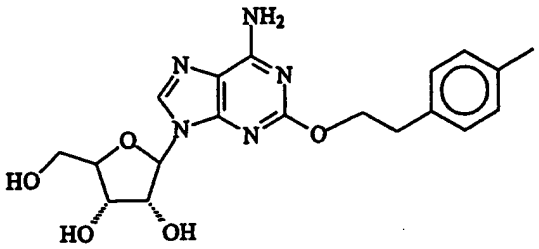
Specific examples of such compounds of formula (I) include WRC-0470, WRC-0474 [SHA 211], WRC-0090 and WRC-0018, shown below:



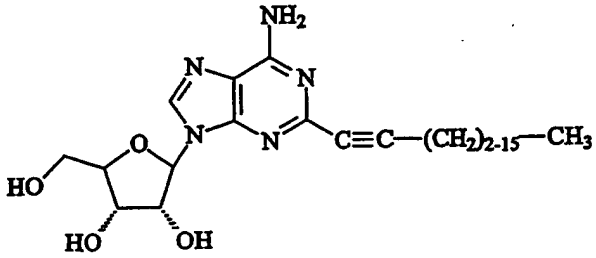
WRC-0470



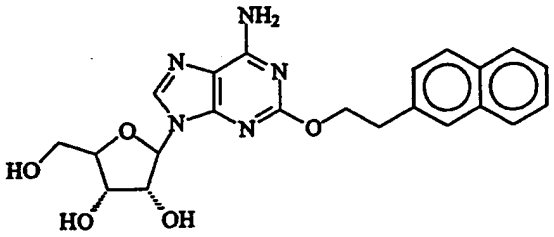
WRC-0474



WRC-0090



and



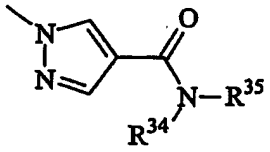
WRC-0018;

wherein the H on CH_2OH can optionally be replaced by ethylaminocarbonyl. Of these specific examples, WRC-0474[SHA 211] and WRC-0470 are particularly preferred.

Such compounds may be synthesized as described in: Olsson et al. (U.S. Pat. Nos. 5,140,015 and 5,278,150); Cristalli (U.S. Pat. No. 5,593,975); Miyasaka et al. (U.S. Pat. No. 4,956,345); Hutchinson, A. J. et al., J. Pharmacol. Exp. Ther., 251, 47 (1989); Olsson, R. A. et al., J. Med. Chem., 29, 1683 (1986); Bridges, A. J. et al., J. Med. Chem., 31, 1282 (1988); Hutchinson, A. J. et al., J. Med. Chem., 33, 1919 (1990); Ukeeda, M. et al., J. Med. Chem., 34, 1334

(1991); Francis, J. E. et al., J. Med. Chem., 34, 2570 (1991); Yoneyama, F. et al., Eur. J. Pharmacol., 213, 199-204 (1992); Peet, N. P. et al., J. Med. Chem., 35, 3263 (1992); and Cristalli, G. et al., J. Med. Chem., 35, 2363 (1992); all of which are incorporated herein by reference.

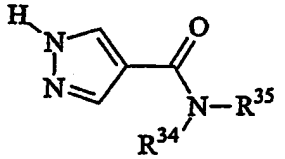
Another embodiment includes compounds having formula (III) where Z^2 is a group having formula (vi):



(vi)

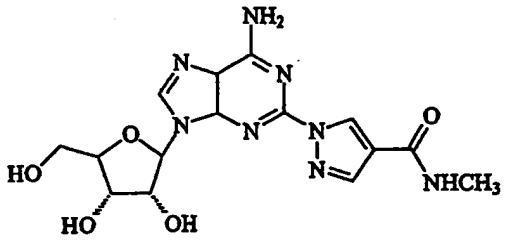
wherein R^{34} and R^{35} are independently H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl, phenyl C_1-C_3 alkyl or R^{34} and R^{35} taken together with the nitrogen atom are a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from nonperoxide oxygen, nitrogen ($N(R^{13})$) or sulphur atoms. Preferably one of R^{34} and R^{35} is hydrogen and the other is ethyl, methyl or propyl. More preferably one of R^{34} and R^{35} is hydrogen and the other is ethyl or methyl.

The 2-(pyrazol-1-yl)adenosine compounds of the invention, wherein Z^2 is a group having formula (vi), can be prepared by reacting a 2-chloro- or 2-iodo adenosine derivative with an 1H-pyrazole-4-carboxamides compound having formula (vii):



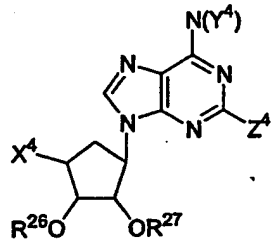
(vii)

where R^{34} and R^{35} are as described above, wherein selective protection/deprotection of the amido group is used as needed. A preferred pyrazole derivative useful in practicing this invention is a compound having the formula:



The 1H-pyrazole-4-carboxamides can be prepared starting with 1H-pyrazole-4-carboxylic acid, available fro m Aldrich Chemical Co. In the first step, the acid is converted to an ester, *e.g.*, a methyl or ethyl ester. The ester converted to the amide via aminolysis, *e.g.*, with methylamine to form the methyl amide. The pyrazole-4-carboxamide will react with the 2-halopurines in the presence of a strong base to provide the 2-(pyrazol-1-yl)adenosine compounds having formula (III).

Another specific group of agonists of A_{2A} adenosine receptors that are useful in the practice of the present invention include compounds having the general formula (IV):



(IV)

wherein Z^4 is $-NR^{28}R^{29}$;

R^{28} is hydrogen or (C_1-C_4) alkyl; and R^{29} is

a) (C_1-C_4) alkyl;

b) (C_1-C_4) alkyl substituted with one or more (C_1-C_4) alkoxy, halogen, hydroxy, amino, mono((C_1-C_4) alkyl)amino, di((C_1-C_4) alkyl)amino or (C_6-C_{10}) aryl wherein aryl is optionally substituted with one or more halogen, hydroxy, amino, (C_1-C_4)alkyl, $R^{30}OOC$-((C_1-C_4)alkyl)-, $R^{31}R^{32}NC(=O)$-((C_1-C_4)alkyl)-, mono((C_1-C_4)alkyl)amino or di((C_1-C_4)alkyl)amino;

c) (C_6-C_{10})aryl; or

d) (C_6-C_{10})aryl substituted with one or more halogen, hydroxy, amino, mono((C_1-C_4)alkyl)amino, di((C_1-C_4)alkyl)amino or (C_1-C_4)alkyl;

wherein each Y^4 is individually H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, phenyl or phenyl(C_1-C_3)alkyl; and X^4 is $-C(=O)NR^{31}R^{32}$, $-COOR^{30}$, or $-CH_2OR^{30}$;

wherein each of R^{31} and R^{32} are independently; hydrogen; C_{3-7}-cycloalkyl; (C_1-C_4)alkyl; (C_1-C_4)alkyl substituted with one or more (C_1-C_4)alkoxy, halogen, hydroxy, $-COOR^{33}$, amino, mono((C_1-C_4)alkyl)amino, di((C_1-C_4)alkyl)amino or (C_6-C_{10})aryl wherein aryl is optionally substituted with one or more halogen, (C_1-C_4)alkyl, hydroxy, amino, mono((C_1-C_4) alkyl)amino or di((C_1-C_4) alkyl)amino; (C_6-C_{10})aryl; or (C_6-C_{10})aryl substituted with one or more halogen, hydroxy, amino, mono((C_1-C_4)alkyl)amino, di((C_1-C_4)alkyl)amino or (C_1-C_4)alkyl;

R^{26} and R^{27} independently represent hydrogen, lower alkanoyl, lower alkoxy-lower alkanoyl, aroyl, carbamoyl or mono- or di-lower alkylcarbamoyl; and R^{30} and R^{33} are independently hydrogen, (C_1-C_4)alkyl, (C_6-C_{10})aryl or (C_6-C_{10})aryl((C_1-C_4)alkyl); or a pharmaceutically acceptable salt thereof.

In one embodiment of formula (IV), at least one of R^{28} and R^{29} is (C_1-C_4)alkyl substituted with one or more (C_1-C_4)alkoxy, halogen, hydroxy, amino, mono((C_1-C_4)alkyl)amino, di((C_1-C_4)alkyl)amino or (C_6-C_{10})aryl wherein aryl is optionally substituted with one or more halogen, hydroxy, amino, (C_1-C_4)alkyl, $R^{30}OOC$-(C_1-C_4)alkyl, mono((C_1-C_4)alkyl)amino or di((C_1-C_4)alkyl)amino.

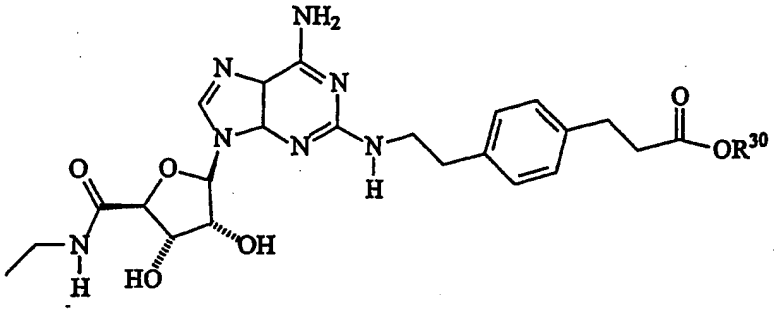
In another embodiment, at least one of R^{31} and R^{32} is C_{1-4}-alkyl substituted with one or more (C_1-C_4)alkoxy, halogen, hydroxy, amino, mono((C_1-C_4)alkyl)amino, di((C_1-C_4)alkyl)amino or C_{6-10}-aryl wherein aryl is optionally substituted with one or more halogen, hydroxy, amino, (C_1-C_4)alkyl, $R^{30}OOC$-(C_1-C_4)alkylene-, mono((C_1-C_4)alkyl)amino or di((C_1-C_4)alkyl)amino.

In another embodiment, at least one of R^{28} and R^{29} is C_{6-10}-aryl substituted with one or more halogen, hydroxy, amino, mono((C_1-C_4)alkyl)amino, di((C_1-C_4)alkyl)amino or (C_1-C_4)alkyl.

In another embodiment, at least one of R^{31} and R^{32} is C_{6-10}-aryl substituted with one or more halogen, hydroxy, amino, mono((C_1-C_4)alkyl)-amino, di((C_1-C_4)alkyl)amino or (C_1-C_4)alkyl.

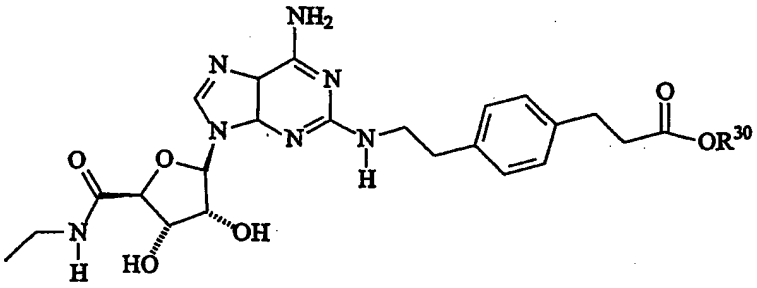
In a preferred combination, R^{31} is hydrogen and R^{32} is (C_1-C_4)alkyl, cyclopropyl or hydroxy-(C_2-C_4)alkyl. A preferred R^{28} group is (C_1-C_4)alkyl substituted with (C_6-C_{10})aryl, that is in turn substituted with $R^{30}O(O)C$-(C_1-C_4)alkyline-.

A preferred compound having formula (IV) is:



wherein R^{30} is hydrogen, methyl, ethyl, n-propyl or isopropyl. More preferred is a compound wherein the R^{30} group is methyl or ethyl. The most preferred R^{30} group is methyl.

Two compounds that are particularly useful in practicing the present invention have the formula:



wherein R^{30} is hydrogen (acid, CGS21680) and where R^{30} is methyl (ester, JR2171).

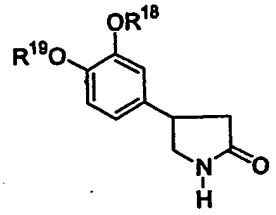
The compounds of the invention having formula (IV) may be synthesized as described in: U.S. Patent 4,968,697 or J. Med. Chem., 33, 1919-1924, (1990)

Specifically, the invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament for treating systemic intoxification in a mammal (e.g. a human),.

Specifically, the invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament for treating inflammation caused by bacterial, fungal or viral infections and the inflammation caused by the treatment of these infections, *e.g.*, by the death of the bacterial or viral cells in a mammal (e.g. a human).

The present method also includes the administration of a Type IV phosphodiesterase (PDE) inhibitor in combination with compounds having formulae (I), (II), (III), and (IV). The combination of the compounds of the invention with type IV phosphodiesterase inhibitor provides synergistic decreases in the inflammatory response of immune cells. Examples of Type IV phosphodiesterase (PDE) inhibitors include those disclosed in U.S. Patent No. 4,193,926, and WO 92-079778, and Molnar-Kimber, K. L. et al., J. Immunol., 150, 295A (1993), all of which are incorporated herein by reference.

Suitable Type IV phosphodiesterase (PDE) inhibitors include racemic and optically active 4-(polyalkoxyphenyl)-2-pyrrolidones of general formula (VI):

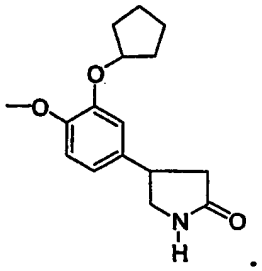


(VI)

(disclosed and described in U.S. Patent No. 4,193,926) wherein R^{18} and R^{19} are independently the same or different and are hydrocarbon radicals having up to 18 carbon atoms with at least one being other than methyl, a heterocyclic ring, or alkyl of 1-5 carbon atoms which is substituted by one or more of halogen atoms, hydroxy, carboxy, alkoxy, alkoxycarbonyl or an amino group or amino.

Examples of hydrocarbon R^{18} and R^{19} groups are saturated and unsaturated, straight-chain and branched alkyl of 1-18, preferably 1-5, carbon atoms, cycloalkyl and cycloalkylalkyl, preferably 3-7 carbon atoms, and aryl and aralkyl, preferably of 6-10 carbon atoms, especially monocyclic.

Rolipram is an example of a suitable Type IV phosphodiesterase or PDE inhibitor included within the above formula. Rolipram has the following formula:



In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Compounds of the present invention can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable excipient. Such pharmaceutical compositions can be prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975). The compounds and compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), topically, orally, or rectally.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance,

tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The compounds or compositions can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal,

and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid

carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The compound is conveniently administered in unit dosage form; for example, containing about 0.05 mg to about 500 mg, conveniently about 0.1 mg to about 250 mg, most conveniently, about 1 mg to about 150 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

The compositions can conveniently be administered orally, sublingually, transdermally, or parenterally at dose levels of about 0.01 to about 150 μg/kg, preferably about 0.1 to about 50 μg/kg, and more preferably about 0.1 to about 10 μg/kg of mammal body weight.

For parenteral administration the compounds are presented in aqueous solution in a concentration of from about 0.1 to about 10%, more preferably about 0.1 to about 7%. The solution may contain other ingredients, such as emulsifiers, antioxidants or buffers.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgment of the attending practitioner.

The preparation of compounds useful in practicing the present invention are disclosed in U.S. Patent Application Serial No. 10/236,379, filed October 1, 2002, and can generally be prepared as illustrated in Schemes 1A and 1B below. Starting materials can be prepared by procedures described in these schemes, procedures described in the General methods below or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in Schemes 1A and Scheme 1B are as defined herein or as in the claims.

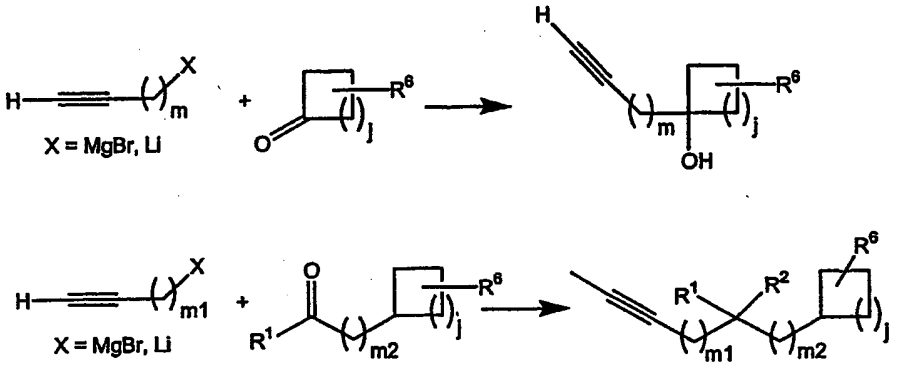
The preparation of alkynyl cycloalkanols is illustrated in Scheme 1A. A solution of an appropriate cycloalkanone (where j is from 0-5) is prepared in a solvent such as THF. A solution of a suitable ethynylmagnesium halide compound in a solvent is added to the cycloalkanone. After addition, the solution is allowed to stir at about 20 C for about 20 hours. The reaction is monitored via TLC until the starting material is consumed. The reaction is quenched with water, filtered over a plug of sand and silica, washed with a solvent, such as EtOAc, and evaporated to provide the product. Typically, two products are formed, the isomers formed by the axial/equatorial addition of the alkyne (where m is as defined above, and the sum of m1and m2 is from 0 to about 7) to the ketone. The compounds are purified via flash chromatography using EtOAc/Hexanes to provide the product.

In accordance with one embodiment of the present invention a composition comprising an agonist of $A_{2A}AR$ is administered to a patient to treat septic shock and systemic inflammatory response syndrome. As used herein the term "treating" includes prophylaxis of the specific disorder or condition, or alleviation of the symptoms associated with a specific disorder or condition and/or preventing or eliminating said symptoms. In one embodiment a method for treating septic shock or systemic inflammatory response syndrome is provided wherein an agonist of $A_{2A}ARs$ is administered to a patient to reduce

inflammation and improve survival in a patient suffering from septic shock or systemic inflammatory response syndrome. In one embodiment the $A_{2A}AR$ agonist is selected from the group consisting of ATL146e, AB-1, AB-3 and JR-3213.

Scheme 1A

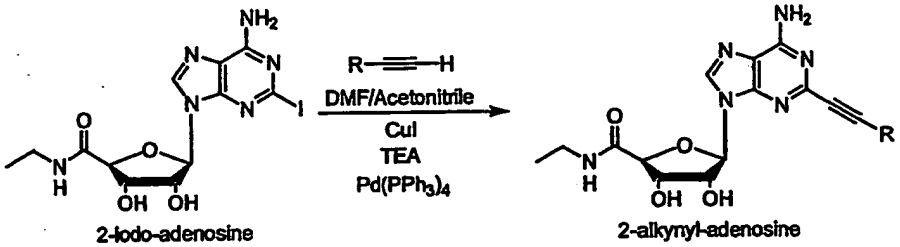
General Route to Synthesis of Alkyne Precursors



The preparation of 2-alkynyladenosines is illustrated in Scheme 1B. A flame-dried round bottom under nitrogen is charged with 5-(6-Amino-2-iodo-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-carboxylic acid ethylamide (NECA 2-Iodoadenosine) and a solvent such as DMF. The appropriate alkyne is added followed by acetonitrile and TEA. (The solvents are degassed.) The appropriate alkyne is added in acetonitrile, followed by TEA, 5 mole % $Pd(PPh_3)_4$, and CuI. The solution is allowed to stir for about 24 hours at room temperature, and monitored until complete by HPLC. If the reaction is not complete after this time, additional catalyst, CuI, and TEA are added. After the reaction is complete, the solvents are removed under high-vacuum and the residue taken up in a small amount of DMF. This product is isolated using preparative silica TLC. The product is purified by RP-HPLC.

Scheme 1B

General Coupling Scheme for the Synthesis of 2-alkynyl-adenosine.



2-Iodo-adenosine 2-alkynyl-adenosine

The following abbreviations have been used herein:

2-Aas	2-alkynyladenosines;
^{125}I-ABA	N^6-(4-amino-3-^{125}iodo-benzyl)adenosine
APCI	Atmospheric pressure chemical ionization
ATL146e	4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxy-tetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl} cyclohexanecarboxylic acid methyl ester;
CCPA	2-chloro-N^6-cyclopentyladenosine;
CGS21680	2-[4-(2-carboxyethyl)phenethylamino]-5'-*N*-ethyl-carboxamidoadenosine;
Cl-IB-MECA	N^6-3-iodo-2-chlorobenzyladenosine-5'-*N*-methylur onamide;
CPA	N^6-cyclopentyladenosine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
EtOAc	ethyl acetate
eq	equivalent

GPCR	G protein coupled receptor; $hA_{2A}AR$, Recombinant human A_{2A} adenosine receptor;
IADO	2-Iodoadenosine
^{125}I-APE,	2-[2-(4-amino-3-[^{125}I]iodophenyl)ethylamino]-adenosine;
NECA	5'-*N*-ethylcarboxamidoadenosine;
IB-MECA	N^6-3-iodobenzyladenosine-5'-*N*-methyluronamide;
2-Iodoadenosine	5-(6-amino-2-iodo-purin-9-yl)-3,4-dihydroxytetra-hydro-furan-2carboxylic acid ethylamide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
^{125}I-ZM241385,	^{125}I-4-(2-[7-amino-2-[2-furyl][1,2,4]triazolo[2,3-*a*]-[1,3,5]triazin-5-yl-amino]ethyl)phenol;
INECA	2-iodo-N-ethylcarboxamidoadenosine
LC/MS	liquid chromatography/mass spectrometry
m.p.	melting point
MHz	megahertz
MRS 1220,	N-(9-chloro-2-furan-2-yl-[1,2,4]triazolo[1,5-c]-quinazolin-5-yl)-2-phenylacetamide;
MS	mass spectrometry
NECA	N-ethylcarboxamidoadenosine
NMR	nuclear magnetic resonance
RP-HPLC	reverse phase high-performance liquid chromatography
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
TBDMSCl	tert-butyldimethylsilylchloride
TEA	triethylamine

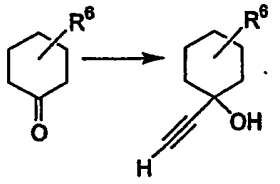
TFA	trifluoroacetic acid
THF	tetrahydrofuan
TLC	thin layer chromatography
p-TSOH	para-toluenesulfonic acid
XAC	8-(4-((2-a-minoethyl)aminocarbonyl-methyloxy)-phenyl)-1-3-dipropylxanthine.

Syntheses of compounds useful in practicing the invention.

All melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra for proton (^{1}H NMR) were recorded on a 300 MHz GE spectrophotometer. The chemical shift values are expressed in ppm (parts per million) relative to tetramethylsilane. For data reporting, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were measured on a Finnigan LcQ Classic. High resolution mass spectrometry (HRMS) data was provided by the Nebraska Center for Mass Spectrometry. Analytical HPLC was done on a Waters 2690 Separation Module with a Waters Symmetry C8 (2.1 x 150 mm) column operated at room temperature. Compounds were eluted at 200 μL/min with 70:30 acetonitrile:water, containing 0.5% acetic acid, with UV detection at 214 nm using a Waters 486 Tunable Detector. Preparative HPLC was performed on a Shimadzu Discovery HPLC with a Shim-pack VP-ODS C_{18} (20 x 100 mm) column operated at room temperature. Compounds were eluted at 30mL/min with a gradient 20-80% of water (containing 0.1% TFA) to methanol over 15 minutes with UV detection at 214 nm using a SPD10A VP Tunable detector. All final compounds presented here were determined to be greater than 98% pure by HPLC. Flash chromatography was performed on Silicyle 60A gel (230-400 mesh) or using reusable chromatography columns and system from RT Scientific, Manchester NH. Analytical thin-layer chromatography was done on Merck Kieselgel 60 F254 aluminum sheets.

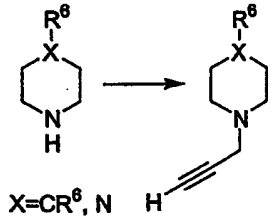
Preparative thin-layer chromatography was done using 1000 micron Analtech Uniplate with silica gel. All reactions were done under a nitrogen atmosphere in flame-dried glassware unless otherwise stated.

General method 1: Preparation of alkynyl cyclohexanols



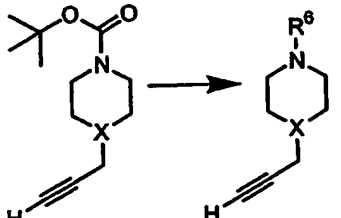
To a solution of about 10 mmol of the appropriate cyclohexanone in about 50 mL of THF is added to about 60 mL (30 mmol) of 0.5 M ethynylmagnesium bromide in THF. The solution is allowed to stir at about 20°C for about 20 hours. After the starting material had been consumed, monitored by TLC, the reaction is quenched with about 5 mL of water, filtered over a plug of sand and silica, washed with EtOAc, and evaporated to yield a yellow oil. Usually the oil contained two spots on TLC with 20% EtOAc/Hexanes, which are visualized with Vanillin. Usually these two products are the different isomers formed by the axial/equatorial addition of the alkyne to the ketone. The compounds are purified via flash chromatography using 10% EtOAc/Hexanes to provide clear oils or white solids in a yield of about 50-80 %.

General method 2: Preparation of propargyl piperadines/piperazines.



To a solution of of the appropriate piperazine/piperadine(about 10.0 mmol), in about 20 mL acetonitrile, is added about 12.0 mmol of propargyl bromide (80% stabilized in toluene) and about 50.0 mmol of anhydrous potassium carbonate. The reaction mixture is filtered, and evaporated to dryness. The resiude is taken up in about 50 mL of dichloromethane/water and the organic layers removed. The aqueous layer is washed with an additional 3 x 25 mL dichloromethane. The organic layer is dried using anhydrous sodium sulfate, filtered, and concentrated to provide the crude product, which is purified using column chromatography.

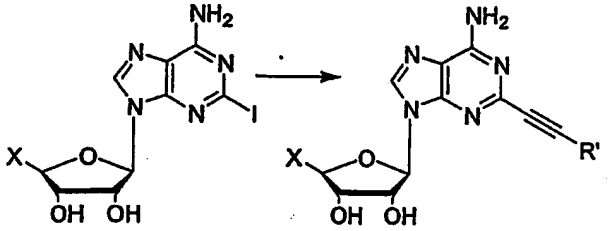
General method 3: Preparation of modified piperadines/piperazines.



X=CR^3, N

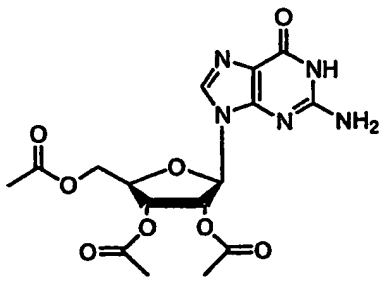
To about 100 mg of the appropriate Boc-protected piperazine/piperadine is added 2-4 mL of neat TFA. The solution is allowed to stir for 6 hours. The TFA is removed under reduced pressure to yield a yellow oil. This oil is taken up in about 10 mL of dichloromethane to which is added 10-fold excess of TEA and 3 equivalents of the appropriate acyl chloride. The yellow solution is allowed to stir at room temperature for about 12 hours, after which time the solvents are removed and the product purified using a 1.1x30 cm 14 g column from Robert Thompson Scientific with a 5%-30% gradient of ethyl acetate/hexanes.

General method 4: Preparation of 2-AAs (2-alkynyladenosines).



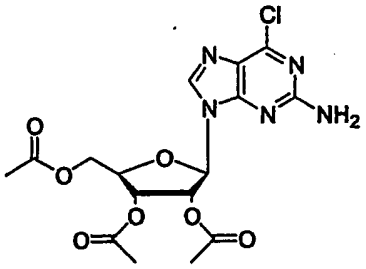
A flame-dried 25 mL round bottom under nitrogen is charged with 5-(6-amino-2-iodo-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (2-Iodoadenosine) (about 40 mg) (X = $CH_3CH_2NHC(O)$-) and dissolved in about 2 mL of DMF. The appropriate alkyne (approx. 0.1mL) is then added followed by about 4mL of acetonitrile and about 0.1mL of TEA. All three solvents had been degassed with nitrogen for at least 24 hours. To this solution is added 5 mole percent $Pd(PPh_3)_4$ and 6 mole % copper iodide. The yellowish solution is allowed to stir for 24 hours at room temperature, or until complete by HPLC. If the reaction is not complete at this time, additional catalyst, CuI, and TEA are added. After the reaction is complete, the solvents are removed under high-vacuum and the red/black residue taken back up in a small amount of DMF. This solution is added to a preparative silica TLC plate (Analtech 1000 microns, 20cm x 20cm) and eluted first with 120 mL of 40% Hexanes/CH_2Cl_2, and then again after addition of 40 mL of MeOH. The UV active band (usually yellow in color) in the middle of the plate is collected, slowly washed with 4 x 25 mL 20% MeOH/CH_2Cl_2, and concentrated. This product is then purified by RP-HPLC.

Preparation 1: [(2R,3R,4R,5R)-3,4-diacetyloxy-5-(2-amino-6-oxohyropurin-9-yl)oxolan-2-yl]methyl acetate (6.2).



A suspension of 113 g (0.4 mol) of dry guanosine (6.1), acetic anhydride (240 mL, 2.5 mol), dry pyridine (120 mL) and dry DMF (320 mL) was heated for 3.75 hours at 75 °C without allowing the temperature to exceed 80 °C. The clear solution was then transferred to a 3L Erlenmyer flask and filled with 2-propanol. Upon cooling the solution to room temperature crystallization was initiated and allowed to proceed at 4 °C overnight. The white solid filtrate was filtered, washed with 2-propanol and recrystallized from 2-propanol to provide 6.2 (96%). ^{1}H NMR (300 Mhz, $CDCl_3$) 8.20 (s, 1H, H-8), 6.17 (d, J = 5.41 Hz, 1 H, H-1) 5.75 (t, J = 5.39 Hz, 1H, H-2), 5.56 (t, J = 5.0, H-3), 4.41 (m, 3H, H-4,5), 2.14 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.10 (s, 3H, Ac). ^{13}C NMR (300 MHz, CD_3OD) 171.0, 170.3, 1702, 157.7, 154.8, 152.4, 136.7, 117.7, 85.5, 80.4, 73.0, 71.3, 64.0, 31.3, 21.2, 21.0.

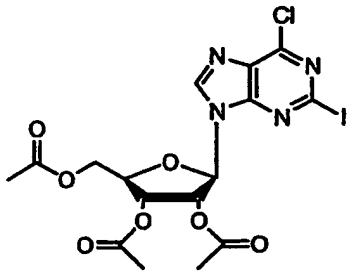
Preparation 2: [(2R,3R,4R,5R)-3,4-diacetyloxy-5-(2-amino-6-chloropurin-9-yl)oxolan-2-yl]methyl acetate (6.3).



To a 1 L flask was added 80 g (0.195 mol) [(2R,3R,4R,5R)-3-4-diacetyloxy-5-(2-amino-6-oxohyropurin-9-yl)oxolan-2-yl]methyl acetate (**6.2**), tetramethylammonium chloride (44 g, 0.4 mol), anhydrous acetonitrile (400 mL) and N,N-dimethlaniline (25 mL). The flask was placed in an ice salt bath and cooled to 2°C. To this solution was added dropwise $POCl_3$ (107 mL 1.15 mol) at a rate that maintained the temperature below 5°C (45 minutes). The flask was then removed from the ice bath, outfitted with a condenser, placed in an oil bath and allowed to reflux for 10 minutes. The solution changed to a red/brown color. The solvent was removed under reduced pressure to yield an oily residue which was transferred to a beaker containing 1000 g of ice and 400 mL of $CHCl_3$ and allowed to stir for 1.5 hours to decompose any remaining $POCl_3$. The organic phase was removed and the aqueous phase extracted with 3 × 50 mL of $CHCl_3$ and pooled with the organic phase. The pooled organic layeres were back extracted with 50 mL of water followed by stirring with 200 mL of saturated $NaHCO_3$. The organic layer was further extracted with $NaHCO_3$ until the aqueous extract was neutral (2X). The organic layer was finally extracted with brine and dried over $MgSO_4$ for 16 hours. To the solution was added 800 mL of 2-propanol after which the solution was concentrated under reduced pressure. To the oily solid was added 200 mL of 2-propanol and the solution was refrigerated overnight. The crystalline

product was filtered, washed, and allowed to dry overnight to give 6.3 (77%). ^{1}H NMR (300 MHz, CD_3OD) 8.31 (s, 1H, H-8), 7.00 (s, 2H, NH_2) 6.06 (d, J= 5.8 Hz, 1H, H-1), 5.83 (t, J= 6.16 Hz, 1H, H-2), 5.67 (m, 1H, H-3), 4.29 (m, 3H, H-4,5), 2.07 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.98 (s, 3H, Ac). ^{13}C NMR (300 MHz, CD_3OD) 171.0, 170.4, 170.2, 160.8, 154.6, 150.8, 142.2, 124.5, 85.8, 80.6, 72.8, 71.2, 63.9, 21.4, 21.3, 21.1.

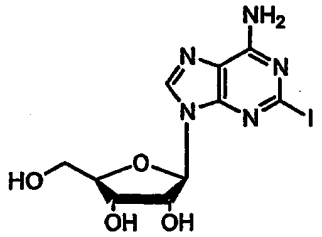
Preparation 3: [(2R,3R,4R,5R)-3,4-diacetyloxy-5-(6-chloro-2-iodopurin-9-yl)oxolan-2-yl]methyl acetate (6.4).



Isoamyl nitrite (5 mL, 37 mmol) was added to a mixture of 5.12 g (12 mmol) [(2R,3R,4R,5R)-3-,4-diacetyloxy-5-(2-amino-6-chloropurin-9-yl)oxolan-2-yl]methyl acetate (**6.3**), I_2 (3.04 g, 12 mmol), CH_2I_2 (10 mL, 124 mmol), and CuI (2.4 g, 12.6 mmol) in THF (60 mL). The mixture was heated under reflux for 45 minutes and then allowed to cool to room temperature. To this solution was added 100 ml of saturated $Na_2S_2O_3$. This step removed the reddish color. The aqueous layer was extracted 3X with chloroform, which was pooled, dried over $MgSO_4$, and concentrated under reduced pressure. The product was then purified over a silica gel column using $CHCl_3$-MeOH (98:2) to collect [(2R,3R,4R,5R)-3,4-diacetyloxy-5-(6-chloro-2-iodopurin-9-yl)oxolan-2-yl]methyl acetate (**6.4**) (80% crystallized from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) 8.20 (s, 1H H-8), 6.17 (d, J = 5.41 Hz, 1H, H-1), 5.75 (t, J= 5.39 Hz, 1H, H-2

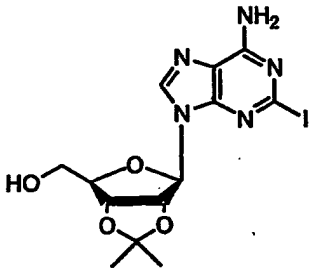
), 5.56 (t, J = 5.40 Hz, 1H, H-3), 4.38 (m, 3H, H-4,5), 2.14 (s, 1H, Ac), 2.11 (s, 1H, Ac), 2.10 (s, 1H, Ac).

Preparation 4: (4S,2R,3R,5R)-2-(6-amino-2-iodopurin-9-yl)-5-(hydroxy-methyl)oxolane-3,4-diol (6.5).



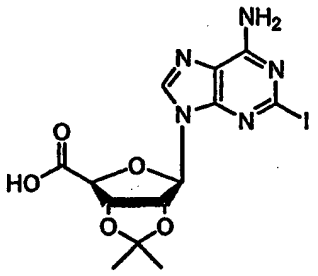
To a flask containing 6.0 g (11.1 mmol) [(2R,3R,4R,5R)-3,4-diacetyloxy-5-(6-chloro-2-iodopurin-9-yl)oxolan-2-yl]methyl acetate (6.4) was added 100 ml of liquid NH_3 at -78°C and the solution was allowed to stir for 6 hours. After which time it was allowed to come to room temperature overnight with concurrent evaporation of the NH_3 to yield a brown oil. The product was crystallized from hot isopropanol to provide 6.5 (80%), m.p. 143-145°C, r.f. = 0.6 in 20% MeOH/$CHCl_3$. ^{1}H NMR (300 MHz, DMSO-d_6) 8.24 (s, 1H), 7.68 (s, 2H), 5.75 (d, J = 6.16, 1H), 5.42 (d, J = 5.40 Hz, 1H), 5.16 (d, J = 4.62 Hz, 1H), 4.99 (t, J = 5.39 Hz, 1H), 4.67 (d, J = 4.81 Hz, 1H), 4.06 (d, J = 3.37 Hz, 1H), 3.89 (m, 1H), 3.54 (m, 2H).

Preparation 5: [(1R,2R,4R,5R)-4-(6-amino-2-iodopurin-9-yl)-7-7-dimethyl-3,6,8-trioxabicyclo[3.3.0]oct-2-yl]methan-1-ol (6.6).



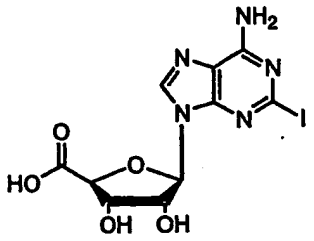
To a solution of 2.0 g (5.08 mmol) (4S,2R,3R,5R)-2-(6-amino-2-iodopurin-9-yl)-5(hydroxymethyl)oxolane-3,4-diol (**6.6**) in 100 mL acetone was added 9.6 g of p-toluenesulfonic acid and 5 ml of dimethoxypropane. The reaction was stirred at room temperature for 1 hour. Solid $NaHCO_3$, 15 g, was added to the solution. The slurry was stirred for an additional 3 hours. The residue was filtered and washed 2X with EtOAc. The filtrate was then concentrated under reduced pressure. The residue was chromatographed on a silica gel column with MeOH-$CHCl_3$ (1:99) to give **6.6** (72%) as a solid, m.p. 185-187°C. ^{1}H NMR (300 MHz, DMSO-d_6) 8.22 (s, 1H, H-8), 7.69 (s, 2H), NH_2), 6.00 (d, J = 2.70 Hz, 1H, H-1), 5.21 (m, 1H, H-2), 5.07 (bs, 1H, OH), 4.88 (m, 1H, H-3), 4.13 (m, 1H, H-4), 3.47 (m, 2H, H-5), 1.49 and 1.28 (s, 3H, $C(CH_3)_2$).

Preparation 6: (2S,1R,4R,5R)-4-(6-amino-2-iodopurin-9-yl)-7,7-dimethyl-3,6,8-trioxabicyclo[3.3.0]octane-2-carboxylic acid (6.7).



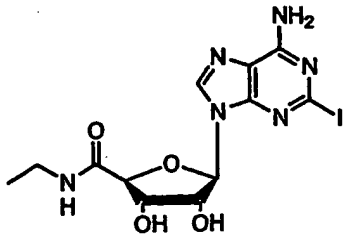
To a stirred solution of 1.6 g (3.7 mmol) of [(1R,2R,4R,5R)-4-(6-amino-2-iodopurin-9-yl)-7-7-dimethyl-3,6,8-trioxabicyclo[3.3.0]oct-2-yl]methan-1-ol **(6.6)** in 200 mL of H_2O was added 0.60 g of KOH and, dropwise, a solution of 1.70 g (10.8 mml) of $KMnO_4$ in 50 mL of H_2O. The mixture was placed in the dark at room temperature for 2-4 days. The reaction mixture was then cooled to 5-10 °C and decolorized by a solution of 4 mL of 30% H_2O_2 in 16 mL of water, while the temperature was maintained below 10 °C using an ice-salt bath. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to about 10 mL and then acidified to pH 4 with 2N HCl. The resulting precipitate was filtered off and washed with ether to yield **6.7** (70%) after drying as a white solid, m.p. 187-190 C. ^{1}H NMR (300 MHz, DMSO-d_6) 8.11 (s, 1H, H-8), 7.62 (s, 2H, NH_2), 7.46 (s, 1H, COOH), 6.22 (s, 1H, H-1), 5.42 (d, J = 5.71 Hz, 1H, H-2), 5.34 (d, J = 6.16 Hz, 1H, H-3), 4.63 (s, 1H, H-4), 1.46 and 1.30 (s, 3H, $C(CH_3)_2$).

Preparation 7: (2S,3S,4R,5R)-5-(6-amino-2-iodopurin-9-yl)-3,4-dihydroxyoxolane-2-carboxylic acid (6.8).



A solution of 1.72 g (3.85 mmol) of (2S,1R,4R,5R)-4-(6-amino-2-iodopurin-9-yl)-7,7-dimethyl-3,6,8-trioxabicyclo[3.3.0]octane-2-carboxylic acid (6.7) in 80 mL of 50% HCOOH was stirred at 80 °C for 1.5 hours. The reaction mixture was evaporated under reduced pressure, dissolved in H_2O, and the solvent was evaporated again. This process was repeated until there was no odor of formic acid in the residue. Recrystallization from water provided 1.33 g (85%) 6.8 as a white solid, m.p. 221-223 °C, dec. ^{1}H NMR (300 MHz, DMSO-d_6) 8.31 (s, 1H, H-8), 7.68 (s, 2H, NH_2), 5.90 (d, J = 6.55 Hz, 1H, H-1), 4.42 (m, 1H, H-2), 4.35 (d, J = 2.31 Hz, 1H, H-4), 4.22 (m, 1H, H-3).

Preparation 8: [(2S,3S,4R,5R)-5-(6-amino-2-iodopurin-9-yl)-3,4-dihydroxyoxolan-2-yl]-N-ethylcarboxamide (6.9).

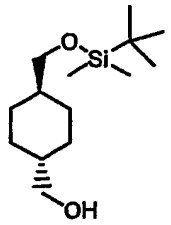


To a cooled (5 °C) and stirred solution of 1.29 g (3.17 mmol) of (2S,3S,4R,5R)-5-(6-amino-2-iodopurin-9-yl)-3,4-dihydroxyoxolane-2-carboxylic

acid (6.8) in 150 mL of absolute ethanol was added dropwise 1.15 mL of ice-cooled $SOCl_2$. The mixture was stirred at room temperature overnight and then brought to pH 8 with saturated aqueous $NaHCO_3$. The mixture was filtered, and then the filtrate was concentrated under reduced pressure to yield a white solid which was dried and then redissolved in 20 mL of dry ethylamine at –20 °C for 3 hours and then at room temperature overnight. The reaction mixture was diluted with absolute ethanol, and the precipitated product was filtered off and washed with dry ether to provide 530 mg (72%) of **6.9** as a pure solid, m.p. 232-234°C. ^{1}H NMR (300 MHz, DMSO-d_6) 8.34 (s, 1H, H-8), 8.12 (t, 1H, NH), 7.73 (s, 2H, NH_2), 5.85, (d, J = 6.93 Hz, 1H, H-1), 4.54 (m, 1H, H-2), 4.25 (d, J = 1.92 Hz, 1H, H-4), 4.13 (m, 1H, H-3), 3.28 (m, 2H, CH_2CH_3), 1.00 (t, J = 7.2 Hz, 3H, CH_2CH_3).

Preparation 9:

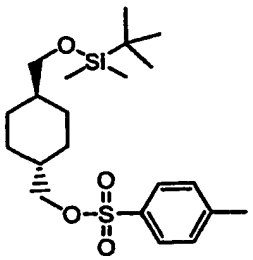
[4-(tert-Butyl-dimethyl-silanyloxymethyl)-cyclohexyl]-methanol (83).



To a 100 mL-flask containing **79** (4.0 g, 27.8 mmol) in DMF (40 mL) was added TBDMSCl (3.56 g, 23.6 mmol) and imidazole (3.79 g, 55.6 mmol). The reaction was allowed to stir at 25 °C for 16hoursafter which time saturated aqueous LiBr (50 mL) was added and the reaction extracted with ether (2 x 50 mL). The ether layers were pooled and extracted again with LiBr (2 x 35 mL). The ether layer became clear. The ether layer was then concentrated *in vacuo* and the product purified by flash chromatography, on a silica gel column, eluting with 1:2 ether/petroleum ether to yield **83** (3.80 g, 62%) as a homogenous oil.

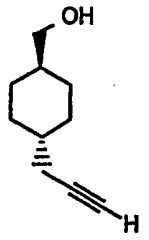
^{1}H NMR ($CDCl_3$) δ 3.46 (d, J = 6.2 Hz, 2 H), 3.39 (d, J = 6.2 Hz, 2 H), 1.95-1.72 (m, 4 H), 1.65 (m, 1 H), 1.40 (m, 1 H), 1.03 – 0.89 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 69.2, 69.1, 41.2, 41.1, 29.5, 26.5, 18.9, -4.8;. APCI *m/z* (rel intensity) 259 (MH^+, 100).

Preparation 10: Toluene-4-sulfonic acid 4-(tert-butyl-dimethyl-silanyloxymethyl)-cyclohexylmethyl ester (84).



To a 100 mL-flask containing 83 (3.4 g, 13.2 mmol) in $CHCl_3$ (30 mL) was added tosyl chloride (3.26 g, 17.1 mmol) and pyidine (3.2 mL, 39.6 mmol). The reaction was allowed to stir at 25 °C for 14hoursafter which time the reaction was concentrated *in vacuo* to yield a wet white solid. To this solid was added ether (50 mL) and the solid was filtered and subsequently washed with additional ether (2 x 50 mL). The ether layers were pooled, concentrated *in vacuo* to yield a clear oil which was purified by flash chromatography, on a silica gel column, eluting with 1:4 ether/petroleum ether to yield 84 (4.5 g, 83 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 7.7, 2 H), 7.33 (d, J = 7.7 Hz, 2 H), 3,81 (d, J = 6.2 Hz, 2H), 3.37 (d, J = 6.2, 2 H), 2.44 (s, 3 H), 1.95-1.72 (m, 4 H), 1.65 (m, 1 H), 1.40 (m, 1 H), 1.03 – 0.89 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 145.1, 133.7, 130.3, 128.4, 75.8, 68.9, 40.7, 38.0, 29.1, 26.5, 22.1, 18.9, -4.9; APCI *m/z* (rel intensity) 413 (MH^+, 100).

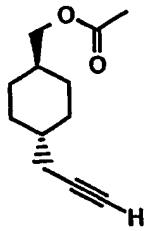
Preparation 11: (4-Prop-2-ynyl-cyclohexyl)-methanol (86).



A 3-neck 250 mL-flask equipped with a gas inlet tube and dry-ice condenser was cooled to –78 °C and charged with liquid ammonia (40 mL). To the reaction mixture was added lithium wire (600 mg, 86.4 mmol) generating a deep blue solution. The mixture was allowed to stir for 1hour. Acetylene, passed through a charcoal drying tube, was added to the ammonia until all the lithium had reacted and the solution turned colorless, at which time the flow of acetylene was stopped, the acetylene-inlet tube and condenser removed and the flask outfitted with a thermometer. DMSO (20 mL) was added and the ammonia evaporated with a warm water bath until the mixture reached a temperature of 30 °C. The solution was stirred at this temperature for 2 hours until the solution stopped bubbling. The mixture was cooled to 5 °C and compound 84 (11.25 g, 27.3 mmol), in DMSO (10 mL), was added. The temperature was maintained at 5 °C. The mixture was allowed to stir at 5 °C for 0.5 hours. Then the solution was gradually warmed to room temperature and stirred for an additional 18 hours. The brown/black reaction mixture was poured slowly over ice (300 g) and extracted with ether (4 x 100 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo* to yield a yellow oil. The oil was subsequently dissolved in THF (200 mL) and changed to a brownish color upon addition of TBAF hydrate (11.20 g, 35.5mmol). The solution was allowed to stir for 24hoursunder N_2 atmosphere. After stirring, the reaction was quenched with water (200 mL) and extracted with ether (3 x 100 mL). The ether extracts were combined and concentrated *in vacuo*. The crude product was purified by chromatography, on a

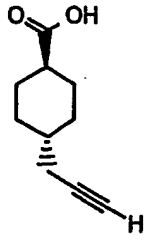
silica gel column, eluting with 1:1 ether/petroleum ether to yield 86 (3.91 g, 93%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.45 (d, J = 6.2, 2 H), 2.10 (d, J = 6.2, 2 H), 1.9 (s, 1 H), 1.94 – 1.69 (m, 4 H), 1.52 – 1.34 (m, 2 H), 1.16 – 0.83 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 83.8, 69.5, 69.0, 40.8, 37.7, 32.3, 29.7, 26.5.

Preparation 12: (4-prop-2-ynylcyclohexyl)methyl acetate (87).



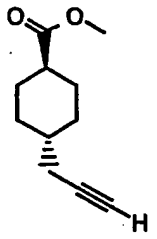
To a solution of 960 mg (6.31 mmol) of **86** in 6 mL DMF was added 0.62 mL (7.57 mmol) pyridine and 0.78 mL (8.27mmol) acetic anhydride. The reaction was allowed to stir overnight at room temperature. After 16 hours, starting material still remained. The reaction mixture was heated at 75 °C for 3 hours. The solvent was removed under reduced pressure to yield a yellow oil which was purified by flash chromatography, on silica gel, eluting with 1:3 ether/petroleum ether to yield 1.12 g (91%) of **87** as an oil. ^{1}H NMR ($CDCl_3$) δ3.87 (d, J = 6.2 Hz, 2 H), 2.06 (d, J = 4.3 Hz, 2 H), 2.03 (s, 3 H), 1.98 – 1.93 (m, 1 H), 1.92 – 1.83 (m, 2 H), 1.83 – 1.74 (m, 2 H), 1.63 – 1.36 (m, 2 H), 1.12 – 0.90 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 171.7, 83.7, 69.9, 69.6, 37.4, 37.3, 32.1, 29.7, 26.5, 21.4; APCI *m/z* (rel intensity) 195 (M^+, 30), 153 (M^+, 70), 135 (M^+, 100).

Preparation 13: 4-prop-2-ynyl-cyclohexanecarboxylic acid (88).



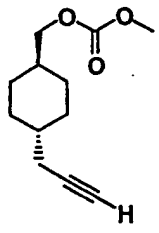
A solution of chromium trioxide (600 mg, 6.0 mmol) in 1.5 M H_2SO_4 (2.6 mL, 150 mmol) was cooled to 5 °C and added to a solution of 86 (280 mg, 1.84 mmol) in acetone (15 mL). The mixture was allowed to warm to room temperature and allowed to stir overnight. Isopropanol (4 mL) was added to the green/black solution, which turned light blue after 1hr. After adding water (15 mL), the solution was extracted with $CHCl_3$ (6 x 25 mL). The organic layers were pooled and concentrated *in vacuo* to yield a white solid. The solid was dissolved in ether (50 mL) and extracted with 1 M NaOH (2 x 30 mL). The basic extracts were pooled, acidified w/ 10% HCl, and re-extracted with ether (3 x 30mL). The ether layers were combined, dried with sodium sulfate and concentrated *in vacuo* to yield a white solid. The product was recrystallized from acetone/water to yield 88 (222 mg, 73%) as white needles: mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 –2.23 (m, 1 H), 2.17 – 2.11 (m, 2 H), 2.07-2.03 (m, 2 H), 1.97 – 1.91 (m, 3H), 1.51-1.39 (m, 3 H), 1.13- 1.01 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 182.5, 83.8, 69.6, 40.7, 37.7, 32.3, 29.6, 26.5; APCI *m/z* (rel intensity) 165 (M$^-$, 100).

Preparation 14: Methyl 4-prop-2-ynylcyclohexanecarboxylate (89).



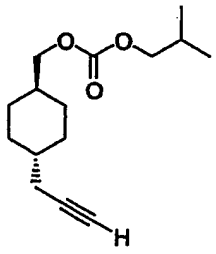
To a solution of 88 (240 mg, 1.45mmol) in 7:3 CH_2Cl_2:MeOH (10 mL) was added TMS Diazomethane (2.0 M in hexanes) (0.9 mL, 1.8 mmol) in 0.2 ml aliquots until the color remained yellow. The reaction was allowed to stir for an additional 0.25 hours at room temperature. After stirring, glacial acetic acid was added dropwise until the solution became colorless. The reaction was concentrated *in vacuo* to an oil which was purified by flash chromatography on silica gel using ether:petroleum ether (1:9) to yield 89 (210 mg, 80%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3H), 2.25 – 2.13 (m, 1 H), 2.08 – 1.94 (m, 3 H), 1.95 – 1.90 (m, 2 H), 1.49 – 1.31 (m, 3 H), 1.10 – 0.93 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 176.7, 83.3, 69.8, 51.9, 43.4, 36.7, 31.9, 29.2, 26.3; APCI *m/z* (rel intensity) 181 (MH^+, 100).

Preparation 15: Trans[4-(1-Propargyl)cyclohexylmethyl] methyl carbonate (90).



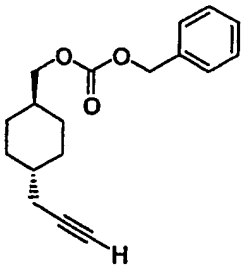
Yield: 345 mg, 81%. ^{1}H NMR ($CDCl_3$) δ 0.98-1.07, 1.40-1.52, 1.57-1.70, 1.78-1.93 (4 x m, 10H, cyclohexyl), 1.96 (t, 1H, acetylene), 2.10 (dd, 2H, -$C_6H_{10}CH_2CCH$), 3.78 (s, 3H, -OCH_3), 3.96 (d, -$C_6H_{10}CH_2O$-).

Preparation 16: Trans[4-(1-Propargyl)cyclohexylmethyl] *iso*-butyl carbonate (91).



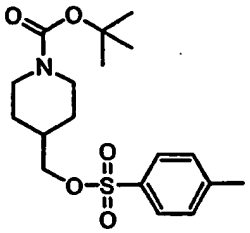
Yield: 433 mg, 83%. ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 4H, -$OCH_2CH(CH_3)_2$), 0.98-1.09, 1.40-1.51, 1.57-1.70, 1.78-1.93 (4 x m, 10H, cyclohexyl), 1.94-2.04 (m, 1H, -$OCH_2CH(CH_3)_2$), 1.96 (t, 1H, acetylene), 2.10 (dd, 2H, -$C_6H_{10}CH_2CCH$), 3.91, 3.95 (2 x d, 4H, -$OCH_2CH(CH_3)_2$, -$C_6H_{10}CH_2O$-).

Preparation 17: Trans[4-(1-Propargyl)cyclohexylmethyl] benzyl carbonate (92).



Yield: 340 mg, 69%. ^{1}H NMR ($CDCl_3$) δ 0.97-1.08, 1.40-1.49, 1.55-1.69, 1.77-1.93 (4 x m, 10H, cyclohexyl), 1.96 (t, 1H, acetylene), 2.10 (dd, 2H, $-C_6H_{10}CH_2CCH$), 3.98 (d, $-C_6H_{10}CH_2O-$), 5.15 (s, 2H, $-OCH_2Ph$), 7.33-7.40 (m, 5H, Ar).

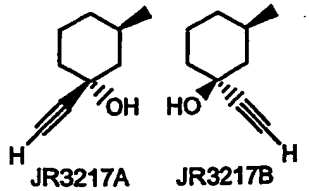
Preparation 18: 4-(Toluene-4-sulfonyloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester (JR3215).



JR3215

A solution of N-Boc-4-piperidinemethanol, 5.0 g (23.2 mmol) in chloroform, 50 mL, was prepared. Toluene sulfonyl chloride, 5.75 g (30.2 mmol), in 5.6 mL of pyridine (69.6 mmol) was added. The solution was stirred under nitrogen allowed to stir for 24 hours. Standard workup and chromatographic purification provided the title compound. Yield 6.0g

Preparation 19: (R)-1-Ethynyl-(R)-3-methyl-cyclohexanol (JR3217A), (S)-1-Ethynyl-(R)-3-methyl-cyclohexanol (JR3217B).

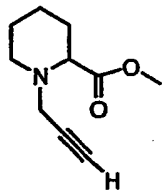


JR3217A JR3217B

To a solution of 1.0 g (8.9 mmol) (R)-(+)-3-methyl-cyclohexanone in 50 mL of THF was added 54 mL (26.7 mmol) of 0.5 M ethynylmagnesium

bromide in THF. The solution was allowed to stir at 20 °C for 20 hours. Analysis by TLC indicated that the starting material had been consumed. The reaction was quenched with 5 mL of water, filtered over a plug of sand and silica, washed with EtOAc, and evaporated to yield 1.15 g of a yellow oil containing two spots (r.f.'s 0.33 (minor, JR3217A) and 0.25 (major, JR3217B), 20% EtOAc/Hexanes) which were visualized with Vanillin. The compound was purified via flash chromatography using 10% EtOAc/Hexanes (225 mL silica) to provide JR3217A and JR3217B.

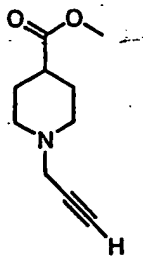
Preparation 20: 1-Prop-2-ynyl-piperidine-2-carboxylic acid methyl ester (JR3249).



JR3249

The title compound was prepared starting with 4.0g (22.3 mmol) of methylpipecolinate hydrochloride according to general method 2.

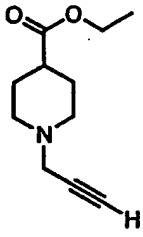
Preparation 21: 1-Prop-2-ynyl-piperidine-4-carboxylic acid methyl ester (JR3245).



JR3245

To a solution of methyl isonipecotate 3.5g (24.4 mmol, 3.30 mL) in 100 mL dichloromethane was added TEA (1.5 eq, 36.6 mmol, 5.1 mL), propargyl bromide (3.0eq, 73.2 mmol, 6.5 ml), at room temperature for 36 hrs. The reaction was quenched with 35 mL water to yield to provide a clear solution. The solution was extracted with dichloromethane 2x25 mL, dried with Na2SO4, and the solvent evaporated to provide a yellow oil. r.f. (40% EtOAc/Hexanes) 0.26 stains faint white with Vanillin, starting material r.f. 0.05 stains yellow with Vanillin. The product appeared pure after extraction.

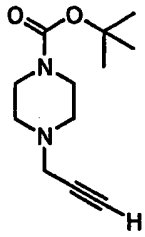
Preparation 22: 1-Prop-2-ynyl-piperidine-4-carboxylic acid ethyl ester (JR3271).



JR3271

The title compound was prepared starting with 2.0g (12.7 mmol) of ethyl isonipecotate according to general method 2.

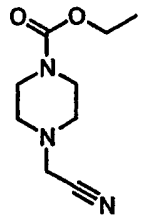
Preparation 23: 4-Prop-2-ynyl-piperazine-1-carboxylic acid tert-butyl ester (JR3275).



JR3275

To a solution of 10.0 g (54.8 mmol) of *tert*-butyl-1-piperazine carboxylate in 60 mL acetonitile was added 5.20 mL (60.4 mmol) propargyl bromide and 37.9 g (274 mmol) anhydrous potassium carbonate. Additional propargy bromide, 1.5mL, was added after stirring for 36 hours at room temperature. The residue was evaporated to dryness. Dichloromethane, 50 mL, and water, 50 mL, were added. The reaction mixture was extracted with CH_2Cl_2, 4 x 40 mL, dried over magnesium sulfate, and evaporate to provide a brown oil. The oil was dissolved in dichloromethane and purify with a RT Scientific system using hexane/ethyl acetate gradient to yield 5.5 g (46%) of yellow oil, which ultimately crystallized upon standing.

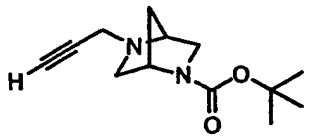
Preparation 24: 4-Cyanomethyl-piperazine-1-carboxylic acid ethyl ester (JR3287).



JR3287

To a solution of 3g (19.0 mmol) of ethyl N-piperazinecarboxylate in 25 mL of CH_3CN was added 1.57g (1.32 mL 20.1mmol) of 2-chloroacetonitrile and 15.6g (95mmol) $K_2CO_3 \cdot 1\frac{1}{2}H_2O$. The suspension was stirred at room temperature for 16 hours. The reaction was analyzed using TLC (35% Ethyl acetate/Hexanes, product r.f. 0.38 vs. sm r.f. of 0.02). The analysis indicated the reaction was complete. The golden yellow solution was evaporated to dryness. The residue was extracted with CH_2Cl_2/H_2O, dried with $MgSO_4$, and concentrated.

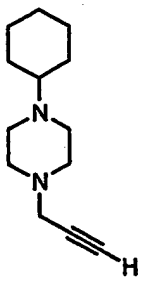
Preparation 25: 5-Prop-2-ynyl-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (JR4013).



JR4013

The title compound was prepared starting with 500 mg (2.52mmol) of 2,5-Diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester according to general method 2.

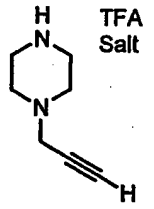
Preparation 26: 1-Cyclohexyl-4-prop-2-ynyl-piperazine (JR4019).



JR4019

The title compound was prepared starting with 3g (17.9 mmol) of 1-cyclohexylpiperazine according to general method 2

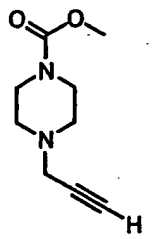
Preparation 27: 1-Prop-2-ynyl-piperazine (JR4029).



JR4029

To a flame-dried 25 mL round bottom flask under nitrogen was added 2.1 g of 4-Prop-2-ynyl-piperazine-1-carboxylic acid *tert*-butyl ester. To this solid was added 5 mL of 98% TFA in 1 mL portions. The solution turned wine red, bubbled and smoked. The additional portions of TFA were added when this activity subsided. After the third portion of TFA had been added only minimal bubbling occurred. The solution was allowed to stir under nitrogen at room temperature for an additional hour and evaporated under reduced pressure to yield the product as a thick red syrup. Assumed quantitative yield of 1.16 g. The residue was suspended in 20 mL dichloromethane and used immediately without further purification for the preparation of compounds JR4031, JR4033, and JR4035.

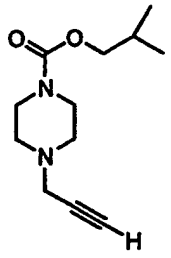
Preparation 28: 4-Prop-2-ynyl-piperazine-1-carboxylic acid methyl ester (JR4031).



JR4031

The title compound was prepared starting with 385 mg (3.1 mmol) of JR4029 and using methylchloroformate according to general method 3.

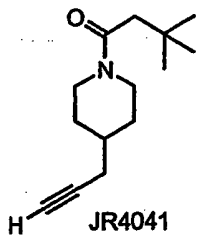
Preparation 29: 4-Prop-2-ynyl-piperazine-1-carboxylic acid isobutyl ester (JR4035).



JR4035

The title compound was prepared starting with 385 mg (3.1 mmol) of JR4029 and using isobutylchloroformate according to general method 3.

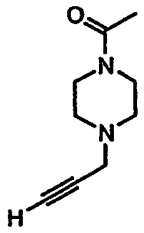
Preparation 30: 3,3-Dimethyl-1-(4-prop-2-ynyl-piperidin-1-yl)-butan-1-one (JR4041).



JR4041

The title compound was prepared starting with *tert*-butyl ester (JR3257) and using *tert*-butylacetylchloride according to general method 3.

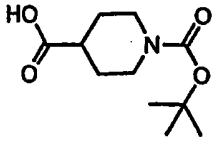
Preparation 31: 1-(4-Prop-2-ynyl-piperazin-1-yl)-ethanone (JR4043).



JR4043

The title compound was prepared starting with 385 mg (3.1 mmol) of JR4029 and using acetyl chloride according to general method 3.

Preparation 32: Piperidine-1,4-dicarboxylic acid mono-tert-butyl ester.



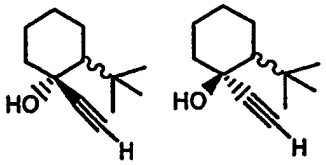
JR3183

To a solution of piperidine-4-carboxylic acid (10 g, 77.5 mmol) and potassium carbonate (21.4 g, 155 mmol) in 150 mL of water was prepared. A solution of di-tert-butyl dicarbonate (16.9g, 77.5 mmol) in 40 mL of THF was added dropwise via addition funnel at 0 °C. The reaction was allowed to warm to room temperature gradually over 30 minutes and stirred for an additional 4 hours. The THF was removed under reduced pressure and the aqueous phase extracted with 50 mL of ether. The aqueous phase was then adjusted to pH 2 with 10 % HCl and extracted with EtOAc, 4 x 50 mL. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to yield 17.2 g (97%) of JR3183 as a white solid. Rf = 0.2 (35% EtOAc/Hexanes stained w/ vanillin). ^{1}H NMR ($CDCl_3$) δ 11.83 (s, 1 H), 3.98 (d, J = 11.8 Hz, 2 H), 2.83 (t, J = 11.8, 2 H), 2.46 (m, 1 H), 1.88 (d, J = 12.9hz, 2 H), 1.2 (m, 2 H), 1.42 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 180.0, 154.8, 79.8, 42.9, 40.8, 28.3, 27.7. APCI m/z (rel intensity) M 228.2 (100).

Preparation 33:

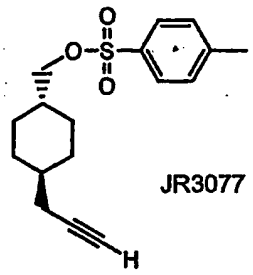
The following intermediate compounds are prepared using the general method 1 described herein and the appropriate starting materials.

(R)-1-Ethynyl-3-*tert*-butyl-cyclohexanol (JR3255A), (S)-1-Ethynyl-3-*tert*-butyl-cyclohexanol (JR3255B).



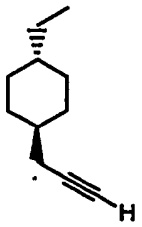
JR3225A JR3225B

Toluene-4-sulfonic acid 4-prop-2-ynyl-cyclohexylmethyl ester (JR3077).



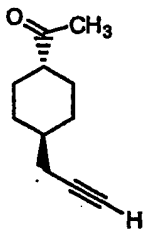
JR3077

1-Ethyl-4-prop-2-ynyl-cyclohexane (JR3083).



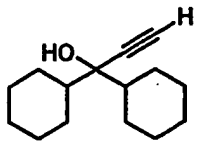
JR3083

1-(4-Prop-2-ynyl-cyclohexyl)-ethanone (JR3115).



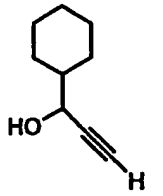
JR3115

1,1-Dicyclohexyl-prop-2-yn-1-ol (JR3127).



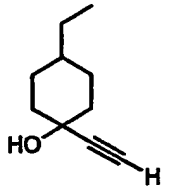
JR3127

1-Cyclohexyl-prop-2-yn-1-ol (JR3129).



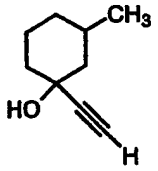
JR3129

4-Ethyl-1-ethynyl-cyclohexanol (JR3143).



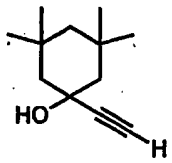
JR3143

1-Ethynyl-3-methyl-cyclohexanol.



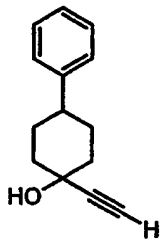
JR3147B

1-Ethynyl-3,3,5,5-tetramethyl-cyclohexanol (JR3151).



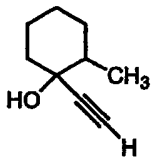
JR3151

1-Ethynyl-4-phenyl-cyclohexanol (JR3153).



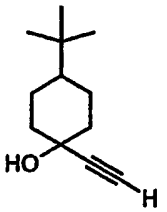
JR3153

1-Ethynyl-2-methyl-cyclohexanol (JR3167B)



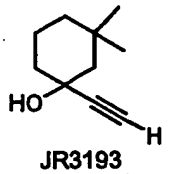
JR3167B

4-tert-Butyl-1-ethynyl-cyclohexanol (JR3191).



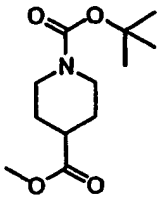
JR3191

1-Ethynyl-3,3-dimethyl-cyclohexanol (JR3193).



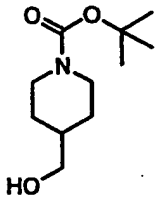
JR3193

Piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester (JR3195).



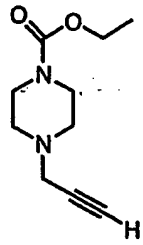
JR3195

4-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (JR3199).



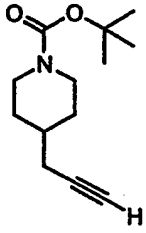
JR3199.

4-Prop-2-ynyl-piperazine-1-carboxylic acid ethyl ester (JR3211).



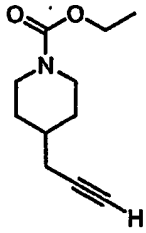
JR3211

4-Prop-2-ynyl-piperidine-1-carboxylic acid tert-butyl ester (JR3257).



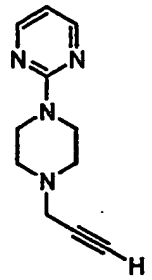
JR3257

4-Prop-2-ynyl-piperidine-1-carboxylic acid ethyl ester (JR3267B).



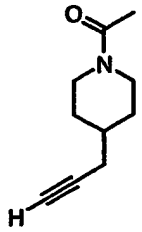
JR3267B

2-(4-Prop-2-ynyl-piperazin-1-yl)-pyrimidine (JR3277).



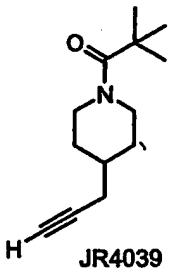
JR3277

1-(4-Prop-2-ynyl-piperidin-1-yl)-ethanone (JR4037).



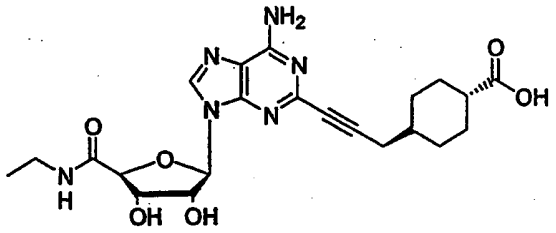
JR4037

2,2-Dimethyl-1-(4-prop-2-ynyl-piperidin-1-yl)-propan-1-one (JR4039).



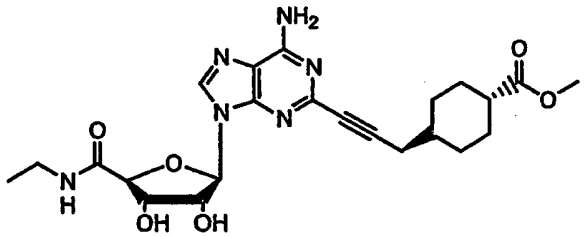
JR4039

Example 1: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-cyclohexanecarboxylic acid (109).



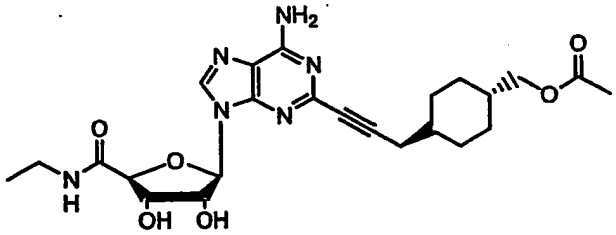
The reaction of **110** with five equivalents of LiOH in THF/water for 6 hours gave **109** (7 mg, 72%) as a white solid which was crystallized from MeOH/H_2O(0.1% TFA) after purification by reverse phase HPLC. ^{1}H NMR (DMSO-d6) δ 8.70 (s, 1 H), 8.41 (s, 1 H), 7.62 (s, 2 H), 5.89 (d, J = 7.25 Hz, 1 H), 4.53 (m, 1 H), 4.27 (s, 1 H), 4.08 (d, J = 3.6 Hz, 1 H), 2.29 (d, J = 6.4 Hz, 2 H), 2.15-1.99 (m, 1 H), 1.92- 1.76 (m, 4 H), 1.52 –1.38 (m, 1 H), 1.38 – 1.19 (m, 2 H), 1.02 (t, J = 6.3 Hz 3 H); ^{13}C NMR (DMSO-d6) 176.7, 169.2, 155.6, 148.9, 145.2, 141.6, 119.0, 87.7, 85.0, 84.6, 81.6, 73.1, 71.9, 43.2, 35.9, 33.3, 31.2, 28.3, 25.6, 15.0. HRMS (FAB) m/z 474.2196 [$(M + H)^+$ cacld for $C_{22}H_{29}N_6O_6$ 474.2182].

Example 2: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4- dihydroxytetrahydro-furan -2-yl)-9H-purin-2-yl]-prop-2-ynyl}-cyclohexanecarboxylic acid methyl ester (110).



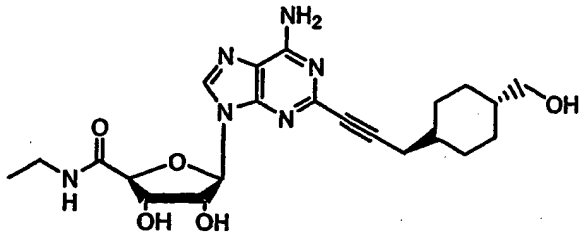
The reaction of 89 with 2-IodoNECA under the general conditions described above provided 110 (74 mg, 60%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.23 (s, 1 H), 5.92 (d, J = 7.7 Hz, 1 H), 4.69 – 4.65 (dd, J = 7.7 Hz, 4.6 Hz, 1 H), 4.40 (s, 1 H), 4.24 (d, J = 4.6 Hz, 1 H), 3.59 (s, 3 H), 3.49 –3.31 (m, 2 H), 2.31 (d, J = 6.6 Hz, 2 H), 2.10 – 2.09 (m, 1 H), 2.01 –1.89 (m, 4 H), 1.61 - 1.32 (m, 5 H), 1.13 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (CD_3OD) δ 177.1, 171.1, 156.3, 149.3, 146.7, 142.4, 119.7 89.6, 86.0, 85.5, 81.6, 74.0, 72.2, 51.2, 43.2, 36.8, 34.2, 31.8, 28.9, 26.2, 14.4; HRMS (FAB) m/z 487.2325 $[(M+H)^+$ cacld for $C_{23}H_{31}N_6O_6$ 487.2305].

Example 3: Acetic acid 4-{3-[6-amino-9-(5-ethylcarbamoyl-3,4- dihydroxy-tetrahydrofuran -2-yl)-9H-purin-2-yl]-prop-2-ynyl}-cyclohexylmethyl ester (111).



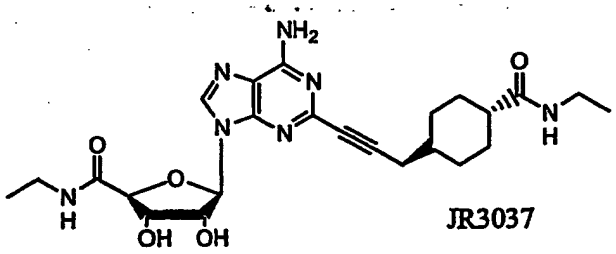
The reaction of 87 with 2-IodoNECA under the general conditions described above gave 111 (78 mg, 62%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.22 (s, 1 H), 5.92 (d, J = 8.1 Hz, 1 H), 4.70 – 4.66 (dd, J = 8.1 Hz, 4.6 Hz, 1 H), 4.40 (d, J = 1.2 Hz, 1 H), 4.25 – 4.23 (dd, J = 4.6 Hz, 1.2 Hz, 1 H), 3.83 (d, J = 6.5, 2 H), 3.53 – 3.31 (m, 2 H), 2.29 (d, J = 6.5 Hz, 2 H), 1.97 (s, 3 H), 1.93 – 1.89 (m, 2 H), 1.79 – 1.75 (m, 2 H), 1.64 – 1.42 (m, 2 H), 1.12 (t, J = 7.3 Hz, 3 H), 1.09 – 0.91 (m, 4 H); ^{13}C NMR (CD_3OD) δ 172.0, 171.2, 156.2, 149.3, 146.7, 142.5, 119.7, 89.6, 86.3, 85.5, 81.5, 74.0, 72.2, 69.6, 37.4, 37.2, 34.2, 32.1, 29.4, 26.4, 19.9, 14.5; HRMS (FAB) m/z 501.2469 $[(M+H)^+$ cacld for $C_{24}H_{33}N_6O_6$ 501.2462].

Example 4: 5-{6-Amino-2-[3-(4-hydroxymethyl-cyclohexyl)-prop-1-ynyl]-purin-9-yl}-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (112).



The reaction of **86** (30 mg, 0.2 mmol) with 2-IodoNECA (28 mg, 0.07 mmol) under the general conditions described above gave **112** (7 mg, 24%) as a white solid. ^{1}H NMR (CD_3OD) δ 8.22 (s, 1 H), 5.92 (d, J = 7.7 Hz, 1 H), 4.70 – 4.66 (dd, J = 7.7 Hz, 4.8 Hz, 1 H), 4.40 (d, J = 1.2 Hz, 1 H), 4.25 – 4.23 (dd, J = 4.8 Hz, 1.2 Hz, 1 H), 3.51 – 3.37 (m, 2 H), 3.31 (d, J = 6 Hz, 2 H), 2.30 (d, J = 6.8 Hz, 2 H), 1.94 – 1.89 (m, 2 H), 1.83 – 1.78 (m, 2 H), 1.64 – 1.42 (m, 2 H), 1.12 (t, J = 7.3 Hz, 3 H), 1.09 – 0.91 (m, 4 H); ^{13}C NMR (CD_3OD) δ 170.3, 155.4, 148.5, 146.0, 141.6, 118.8, 88.7, 85.5, 84.6, 80.6, 73.1, 71.3, 66.8, 39.6, 36.9, 33.3, 31.5, 28.6, 25.6, 13.5; HRMS (FAB) m/z 459.2373 [$(M + H)^+$ cacld for $C_{22}H_{31}N_6O_5$ 459.2356].

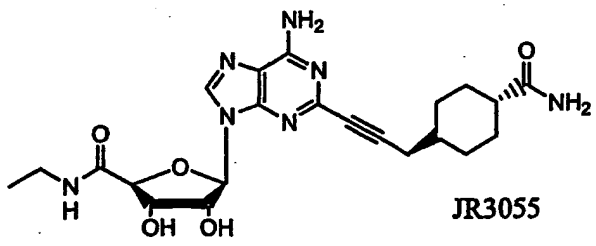
Example 5: 5-{6-Amino-2-[3-(4-ethylcarbamoyl-cyclohexyl)- prop-1-ynyl]-purin -9-yl}-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3037).



JR3037

To a sealed tube containing 5 mL of freshly distilled ethylamine was added 10 mg (0.02 mmol) of ATL146e. The flask was sealed and allowed to stir at 60°C for 80hours. After this time the reaction was only about 50% complete by HPLC. The vessel was cooled to 0°C, opened, and the ethylamine was removed in vacuo to yield 4.5 mg (73%) of JR3037 as a white solid and the recovery of 4.0 mg of starting material after the residue was purified by RP-HPLC. ^{1}H NMR (CD_3OD-d_4) δ. ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 500.8 (MH^+, 100), 327.4(3).

Example 6: 5-{6-Amino-2-[3-(4-carbamoyl-cyclohexyl)- prop-1-ynyl]purin -9-yl}-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3055).

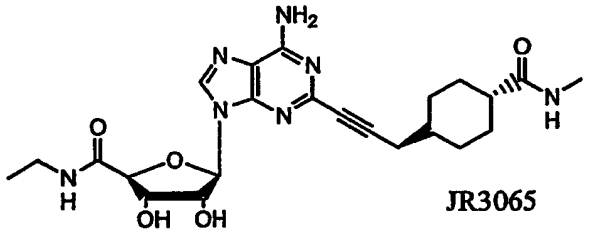


JR3055

To a sealed tube containing 10 mL of saturated $MeOH/NH_3$ solution was added 5 mg (0.01 mmol) of ATL146e. The flask was sealed and allowed to

stir at 25°C for 48hours. The vessel was cooled to 0°C, opened, and the ammonia removed by bubbling N_2 for 1 hour. The remaining solvent was then removed in vacuo to yield 4.0 mg (83%) of JR3055 as a white solid after the residue was purified by RP-HPLC. ^{1}H NMR (CD_3OD-d_4) δ 8.41 (s, 1 H), 5.98 (d, J = 7.2 Hz, 1H), 4.65 (dd, J = 7.3 Hz, 4.8 Hz, 1 H), 4.41 (d, J = 2.0 Hz, 1 H), 4.28 (dd, J = 4.6 Hz, 2.0 Hz, 1 H), 3.35 (m, 2 H), 2,37 (d, J= 6,4 Hz, 2 H) 2.10 (m, 1 H), 1.90 (m, _ H), 1.53 (m, _ H_), 1.23 (m, _ H), 1,12 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 472.3 (MH^+, 100), 299.4(10).

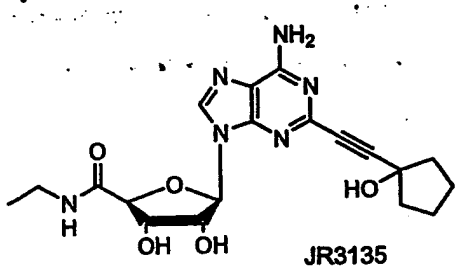
Example 7: 5-{6-Amino-2-[3-(4-methylcarbamoyl-cyclohexyl)- prop-1-ynyl]purin -9-yl}-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3065).



JR3065

To a sealed tube containing 10 mL 2.0 M methylamine in methanol was added 16.5 mg (0.03 mmol) of ATL146e. The flask was sealed and allowed to stir at 70°C for 120hours. The vessel was cooled to 0°C, opened, and the solvent was removed in vacuo to yield 8.0 mg (48%) of JR3065 as a white solid after the residue was purified by RP-HPLC. ^{1}H NMR (CD_3OD-d_4) δ. ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 486.3 (MH^+, 100), 313.4(35).

Example 8: 5-[6-Amino-2-(1-hydroxy-cyclopentylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3135).



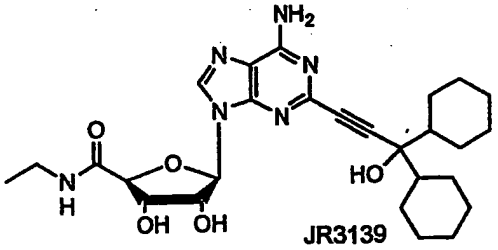
JR3135

The title compound was prepared using the appropriate starting materials and procedures described herein. The results are as follows:

^{1}H NMR (CD_3OD-d_4) δ 8.48 (s, 1 H), 6.04 (d, J = 6.9 Hz, 1 H), 4.72 (dd, J = 6.9 Hz, J = 4.4 Hz, 1 H), 4.46 (d, J = 2.3 Hz, 1 H), 4.33 (dd, J = 4.6 Hz, J = 1.9 Hz, 1 H), 3.42 (m, 2 H), 2.04 (m, 4 H), 1.83, (m, 4 H), 1.16 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (CD_3OD-d_4) δ 171.9, 155.3, 150.0, 144.3, 120.6, 95.4, 90.6, 89.5, 86.2, 79.9, 74.9, 74.0, 70.5, 42.9, 35.3, 24.4, 15.3. APCI m/z (rel intensity) 417.2 (MH^+, 100), 399.4(85), 244.3(15), 26.5(25). HRMS M^+ actual 417.18864, observed 417.18880.

Example 9:

5-[6-Amino-2-(3,3-dicyclohexyl-3-hydroxy-prop-1-ynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3139).



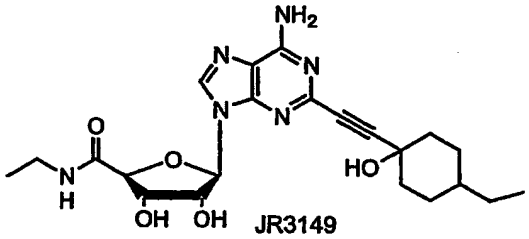
JR3139

The title compound was prepared using the appropriate starting materials and procedures described herein. The results are as follows:

^{1}H NMR (CD_3OD-d_4) δ 8.57 (s, 1 H), 6.09 (d, J = 6.6 Hz, 1 H), 4.77 (dd, J = 6.7, Hz, J = 4.8 Hz, 1 H), 4.46 (d, J = 2.3 Hz, 1 H), 4.37 (dd, J = 4.6 Hz, J = 2.3 Hz, 1 H), 3.42 (m, 2 H) 1.80 (m, 13 H), 1.28 (m, 9 H), 1.13 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 527.3 (MH^+, 60), 509.5(100), 354.4(5), 336.5(5), 279.5(8). HRMS M^+ actual 527.29819, observed 527.29830

Example 10:

5-[6-Amino-2-(4-ethyl-1-hydroxy-cyclohexylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3149).



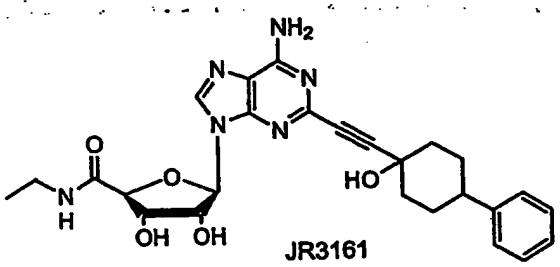
JR3149

The title compound was prepared using the appropriate starting materials and procedures described herein. The results are as follows:

^{1}H NMR (CD_3OD-d_4) δ 8.51 (s, 1 H), 6.06 (d, J = 7.0 Hz, 1 H), 4.75 (dd, J = 6.4 Hz, J = 4.9 Hz, 1 H), 4.46 (d, J = 1.9 Hz, 1 H), 4.34 (dd, J = 4.9 Hz, J = 2.1 Hz, 1 H), 3.42 (m, 2 H), 2.12 (d, J = 11.9 Hz, 2 H), 1.80 (d, J = 11.9 Hz, 2 H), 1.58 (t, J = 12.1 Hz, 2 H), 1.28 (m, 4 H), 1.15 (t, J = 7.1 Hz, 3 H), 0.91 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (CD_3OD-d_4) δ 171.9, 155.4, 150.0, 144.2, 143.8, 120.6, 94.5, 90.5, 86.1, 81.8, 74.9, 74.1, 70.3, 40.5, 39.8, 35.3, 31.0, 30.2, 15.2, 12.0. APCI m/z (rel intensity) 459.4 (MH^+, 100), 441.4(60), 268.4(10). HRMS M^+ actual 459.23559, observed 459.23550.

Example 11:

5-[6-Amino-2-(1-hydroxy-4-phenyl-cyclohexylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3161).



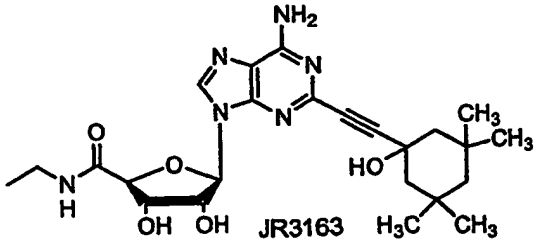
JR3161

The title compound was prepared using the appropriate starting materials and procedures described herein. The results are as follows:

^{1}H NMR (CD_3OD-d_4) δ 8.45 (s, 1 H), 7.26 (m, 4 H), 7.14 (m, 1 H), 6.05 (d, J = 7.3 Hz, 1 H), 4.80 (dd, J = 7.3 Hz, J = 4.8 Hz, 1 H), 4.46 (d, J = 1.6 Hz, 1 H), 4.34 (dd, J = 4.7 Hz, J = 1.8 Hz, 1 H), 3.44 (m, 2 H), 2.58 (m, 1 H), 2.23 (d, J = 11.7 H, 2 H), 1.92 (m, 4 H), 1.78, (m, 2 H), 1.15 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 507.3 (MH^+, 100) 489.4(70), 334.3(5), 316.5(8). HRMS M^+ actual 507.23559, observed 507.23580.

Example 12:

5-[6-Amino-2-(1-hydroxy-3,3,5,5-tetramethyl-cyclohexylethynyl)purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3163).

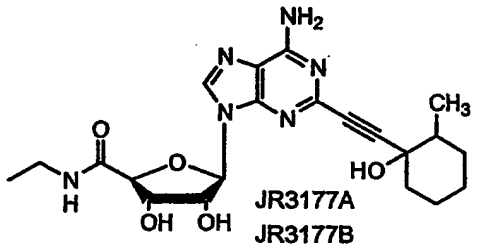


JR3163

The title compound was prepared using the appropriate starting materials and procedures described herein. The results are as follows:

^{1}H NMR (CD_3OD-d_4) δ 8.54 (s, 1 H), 6.04 (d, J = 6.9 Hz, 1 H), 4.74 (dd, J = 6.9 Hz, J = 5.0 Hz, 1 H), 4.46 (d, J = 1.9 Hz, 1 H), 4.34 (dd, J = 4.7 Hz, J = 1.9 Hz, 1 H), 3.44 (m, 2 H), 1.74 (s, 4 H), 1.13 (m, 17 H). APCI m/z (rel intensity) 487.3 (MH^+, 75), 469.4(100), 296.4 (10).

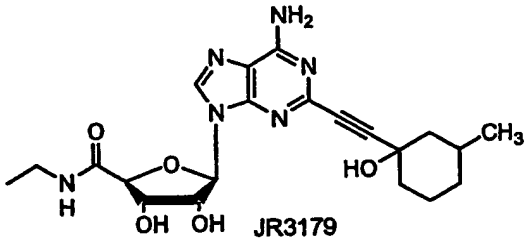
Example 13: 5-[6-Amino-2-(1-hydroxy-2-methyl-cyclohexylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3177A, JR3177B).



JR3177A
JR3177B

The reaction of 1-Ethynyl-2-methyl-cyclohexanol (JR3169B) (100 mg, 0.72 mmol) with 2-iodo-NECA (25 mg, 0.06 mmol) under the general coupling conditions gave JR3177A (8.0 mg) and JR3177B (8.2 mg) (overall yield 65%) as white solids after purification by a silica plug and RP-HPLC. JR3177A: ^{1}H NMR (CD_3OD-d_4) δ 8.47 (s, 1 H), 6.05 (d, J = 6.9 Hz, 1 H), 4.77 (dd, J = 6.9 Hz, J = 4.9 Hz, 1 H), 4.45 (d, J = 1.9 Hz, 1 H), 4.34 (dd, J = 4.6 Hz, J = 2.1 Hz, 1 H), 3.41 (m, 2 H), 2.13 (d, J = 12.7 Hz, 2 H), 1.65 (m, 5 H), 1.32 (m, 2 H), 1.14 (t, J = 7.0 Hz, 3 H), 1.13 (d, J = 6.6 Hz, 3 H).. ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 445.3 (MH^+, 100), 427.4(80), 254.4(14). ^{1}H NMR (CD_3OD-d_4) δ 8.49 (s, 1 H), 6.05 (d, J = 6.9 Hz, 1 H), 4.78 (dd, J = 6.4 Hz, J = 4.9 Hz, 1 H), 4.45 (d, J = 1.9 Hz, 1 H), 4.34 (dd, J = 4.6 Hz, J = 1.6 Hz, 1 H), 3.42 (m, 2 H), 2.12 (d, J = 12.3 Hz, 2 H), 1.65 (m, 4 H), 1.35 (m, 4 H), 1.14 (t, J = 7.3 Hz, 3 H), 1.12 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 445.7 (MH^+, 100), 427.3(35), 254.4(3.5).

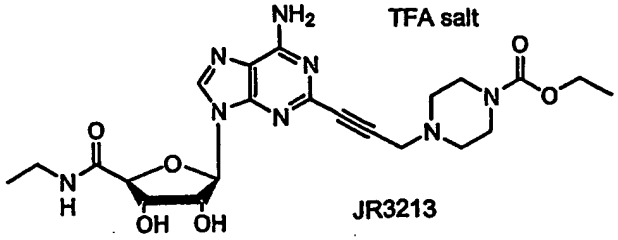
Example 14: 5-[6-Amino-2-(1-hydroxy-3-methyl-cyclohexylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3179).



JR3179

The reaction of 1-Ethynyl-3-methyl-cyclohexanol (JR3149B) (100 mg, 0.72 mmol) with 2-iodo-NECA (25 mg, 0.06 mmol) under the general coupling conditions gave JR3179 (15.0 mg, 59%) as a white solid after purification by a silica plug and RP-HPLC. ^{1}H NMR (CD_3OD-d_4) δ 8.49 (s, 1 H), 6.06 (d, J = 6.9 Hz, 1 H), 4.75 (dd, J = 6.4 Hz, J = 4.9 Hz, 1 H), 4.46 (d, J = 1.9 Hz, 1 H), 4.34 (dd, J = 4.9 Hz, J = 2.1 Hz, 1 H), 3.42 (m, 2 H), 2.09 (d, J = 12.3 Hz, 2 H), 1.73 (m, 4 H), 1.46 (m, 1 H), 1.23 (m, 1 H), 1.16 9 (t, J = 7.1 Hz, 3 H), 0.95 (d, J = 6.2 Hz, 3 H), 0.89 (m, 1 H). ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 445.3 (MH^+, 100), 427.4(40), 254.4(4).

Example 15: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan -2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperazine-1-carboxylic acid ethyl ester (JR3213).

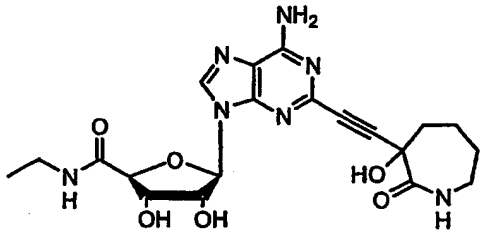


JR3213

The title compound was prepared using the appropriate starting materials and procedures described herein. The results are as follows:

^{1}H NMR (CD_3OD-d_4) δ 8.48 (s, 1 H), 6.00 (d, J = 6.9 Hz, 1 H), 4.67 (dd, J = 6.5 Hz, J = 5.0 Hz, 1 H), 4.42 (d, J = 1.9 Hz, 1 H)), 4.39 (s, 2 H), 4.35 (dd, J = 4.7 Hz, J = 1.9 Hz, 1 H), 4,13 (q,) 3.42 (m, 2 H),. ^{13}C NMR (CD_3OD-d_4) δ. APCI m/z (rel intensity) 503.4 (MH^+, 100), 330.3 (6).

Example 16: 5-[6-Amino-2-(3-hydroxy-2-oxo-azepan-3-ylethynyl)purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3243A, JR3243B).

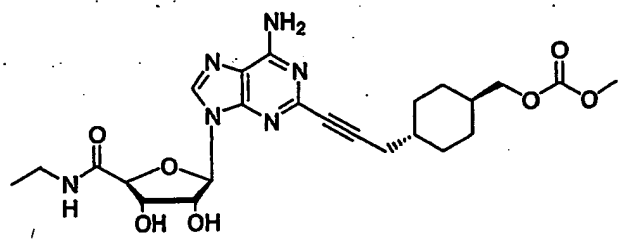


JR3243

35 mg (0.081 mmol) IodoNECA (62mg alkyne, 0.41mmol), 2ml DMF, 4ml Acetonitrile, 0.2ml TEA, d(PPH3)4, CuI. Stirred overnight at room temperature (11/29/01). Rxn is tan w/ brown precipitate. TLC (20%MeOH/CH2Cl2) indicates rxn complete (r.f. INECA = 0.67, r.f. product = 0.45). Filtered mixture through celite, washed with 3x2mL DMF, and evaporated under vacuum to brown oil. (solid precipitates out upon the addition of MeOH, thus used DMF to load on prep plate).

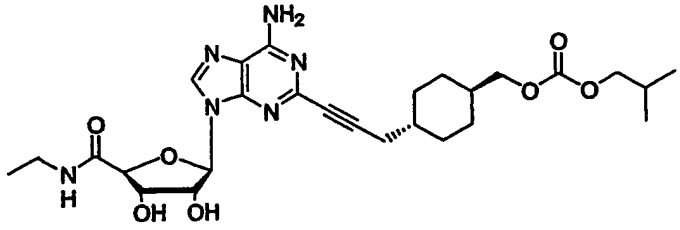
The following compounds can be prepared by following the general method 4 described herein and the appropriate intermediate compounds described herein.

Example 17: N-Ethyl 2-{3-[trans-4-(methoxycarbonyloxamethyl)-cyclohexyl]-1-propyn-1-yl}adenosine-5'-uronamide (ATL214) :



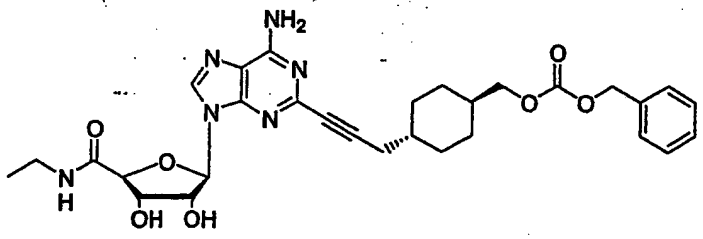
Yield 3.4 mg, 10%. ^{1}H NMR (CD_3OD) δ 1.18 (t, 3H, -NHCH$_2$C*H*$_3$), 1.03-1.20, 1.51-1.70, 1.79-1.85, 1.94-2.01 (4 x m, 10H, cyclohexyl), 2.35 (d, 2H, -C$_6$H$_{10}$C*H*$_2$CC-), 3.46 (m, 2H, -NHC*H*$_2$CH$_3$), 3.73 (s, 3H, -OC*H*$_3$), 3.94 (d, 2H, -C$_6$H$_{10}$C*H*$_2$O-), 4.29 (dd, 1H, 3'-H), 4.45 (d, 1H, 4'-H), 4.72 (dd, 1H, 2'-H), 5.97 (d, 1H, 1'-H), 8.27 (s, 1H, 8-H). APCI *m/z* 517.4 (M+H$^+$).

Example 18: N-Ethyl 2-{3-[trans-4-(isobutoxyoxycarbonyloxamethyl)-cyclohexyl]-1-propyn-1-yl}adenosine-5'-uronamide (ATL215) :



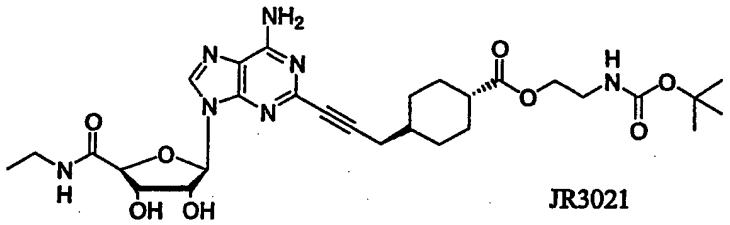
Yield 8.5 mg, 30%. ^{1}H NMR (CD_3OD) δ 0.94 (d, 4H, -OCH$_2$CH(C*H*$_3$)$_2$), 1.18 (t, 3H, -NHCH$_2$C*H*$_3$), 1.04-1.24, 1.54-1.72, 1.79-2.03 (3 x m, 11H, cyclohexyl, -OCH$_2$C*H*(CH$_3$)$_2$), 2.38 (d, 2H, -C$_6$H$_{10}$C*H*$_2$CC-), 3.43 (m, 2H, -NHC*H*$_2$CH$_3$), 3.89, 3.94 (2 x d, 4H, -C$_6$H$_{10}$C*H*$_2$O-, -OC*H*$_2$CH(CH$_3$)$_2$), 4.30 (dd, 1H, 3'-H), 4.46 (d, 1H, 4'-H), 4.71 (dd, 1H, 2'-H), 6.00 (d, 1H, 1'-H), 8.37 (br s, 1H, 8-H). APCI *m/z* 559.5 (M+H$^+$).

Example 19: N-Ethyl 2-{3-[trans-4-(benzoxycarbonyloxamethyl)-cyclohexyl]-1-propyn-1-yl}adenosine-5'-uronamide (ATL216):



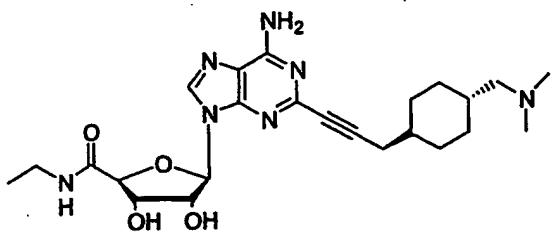
Yield 1.0 mg, 3%. ^{1}H NMR (CD_3OD) δ 1.17 (t, 3H, -NHCH$_2$C*H*$_3$), 1.03-1.23, 1.52-1.71, 1.78-1.86, 1.93-2.02 (4 x m, 10H, cyclohexyl), 2.35 (d, 2H, -C$_6$H$_{10}$C*H*$_2$CC-), 3.45 (m, 2H, -NHC*H*$_2$CH$_3$), 3.97 (d, 2H, -C$_6$H$_{10}$C*H*$_2$O-), 4.29 (dd, 1H, 3'-H), 4.45 (d, 1H, 4'-H), 4.72 (dd, 1H, 2'-H), 5.13 (s, 2H, -OC*H*$_2$Ph), 5.97 (d, 1H, 1'-H), 7.33-7.37(m, 5H, Ar), 8.30 (br s, 1H, 8-H). APCI *m/z* 593.3 (M+H$^+$).

Example 20: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxy-tetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-cyclohexanecarboxylic acid 2-tert-butoxycarbonylamino-ethyl ester.

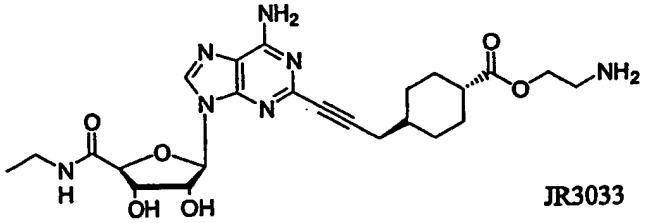


JR3021

Example 21: 5-{6-Amino-2-[3-(4-dimethylaminomethyl-cyclohexyl)-prop-1-ynyl]-purin-9-yl}-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR2023).

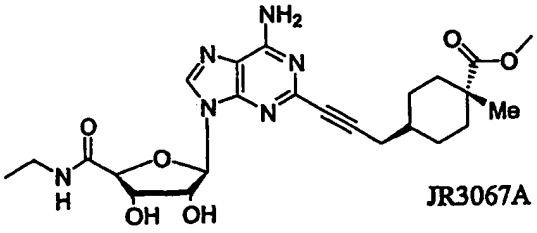


Example 22: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxy-tetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-cyclohexanecarboxylic acid 2-aminoethyl ester (JR3033).



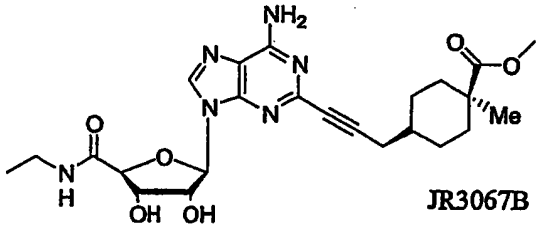
JR3033

Example 23: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-1-methyl-cyclohexanecarboxylic acid methyl ester (JR3067A).



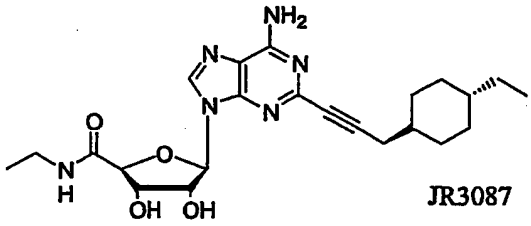
JR3067A

Example 24: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4- dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-1-methyl-cyclohexanecarboxylic acid methyl ester (JR3067B).



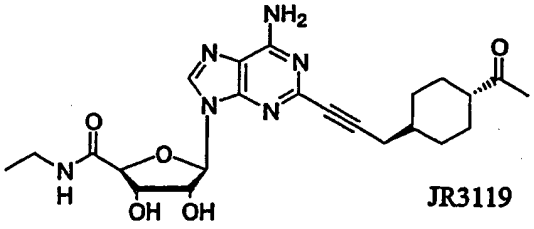
JR3067B

Example 25: 5-{6-Amino-2-[3-(4-ethyl-cyclohexyl)-prop-1-ynyl]-purin-9-yl}-3,4- dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3087)



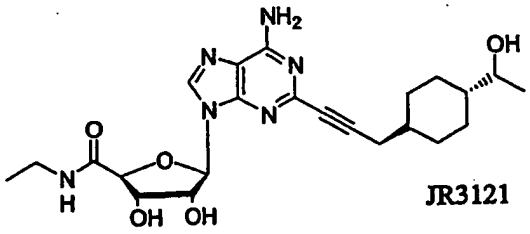
JR3087

Example 26: 5-{2-[3-(4-Acetyl-cyclohexyl)-prop-1-ynyl]-6-aminopurin-9-yl}-3,4- dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3119).



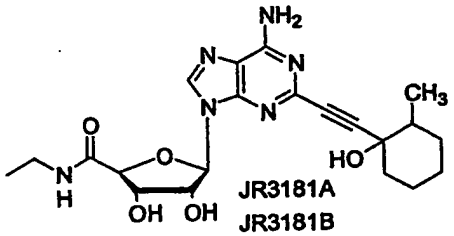
JR3119

Example 27: 5-(6-Amino-2-{3-[4-(1-hydroxy-ethyl)-cyclohexyl]-prop-1-ynyl}-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide.



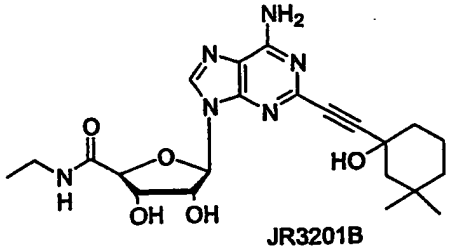
JR3121

Example 28: 5-[6-Amino-2-(1-hydroxy-2-methyl-cyclohexylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3181A, JR3181B).



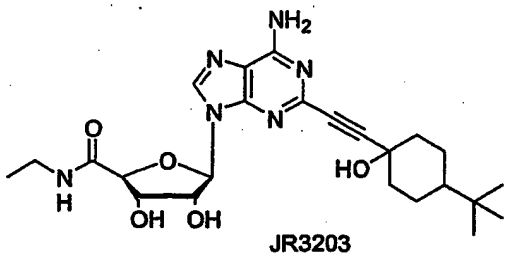
JR3181A
JR3181B

Example 29: 5-[6-Amino-2-(1-hydroxy-3,3-dimethylcyclohexyl-ethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3201B).



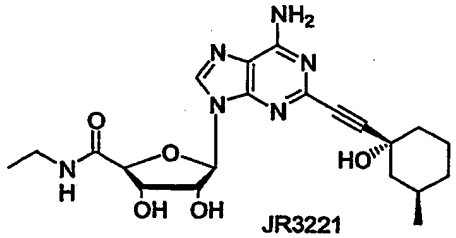
JR3201B

Example 30: 5-[6-Amino-2-(4-tert-butyl-1-hydroxycyclohexylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3203).



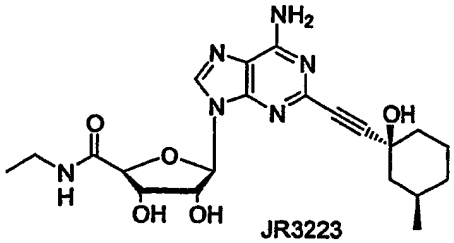
JR3203

Example 31: 5-[6-Amino-2-(1-hydroxy-3-methylcyclohexylethynyl)purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3221).



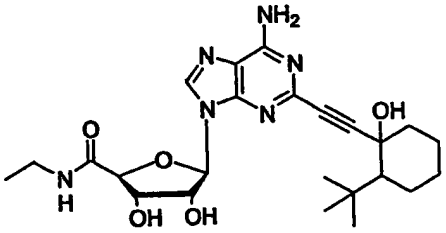
JR3221

Example 32: 5-[6-Amino-2-(1-hydroxy-3-methylcyclohexylethynyl)purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3223, ATL 203).



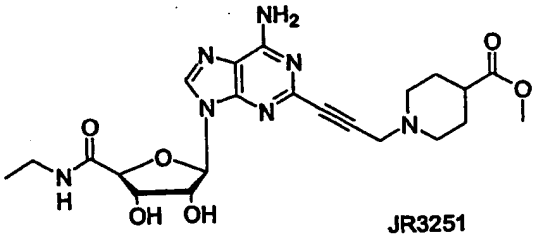
JR3223

Example 33: 5-[6-Amino-2-(2-tert-butyl-1-hydroxycyclohexylethynyl)-purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3227).



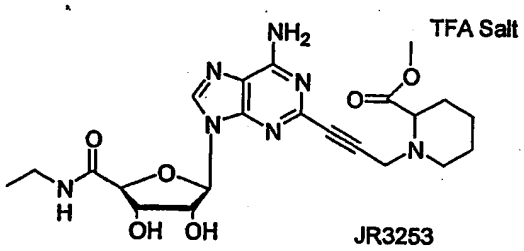
JR3227

Example 34: 1-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-4-carboxylic acid methyl ester (JR3251).



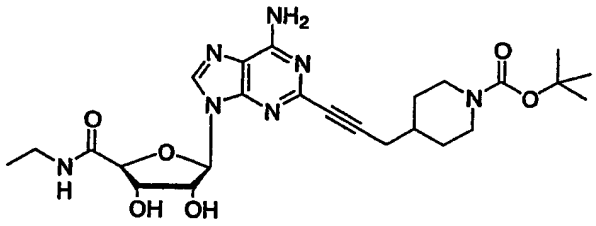
JR3251

Example 35: 1-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4- dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-2-carboxylic acid methyl ester (JR3253).



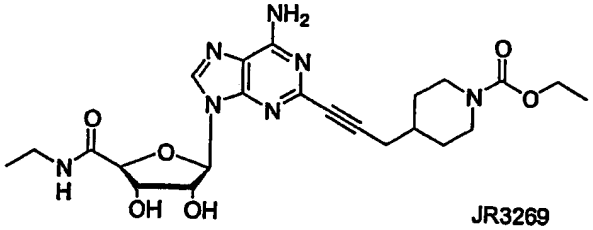
JR3253

Example 36: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4- dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid tert-butyl ester (JR3259).



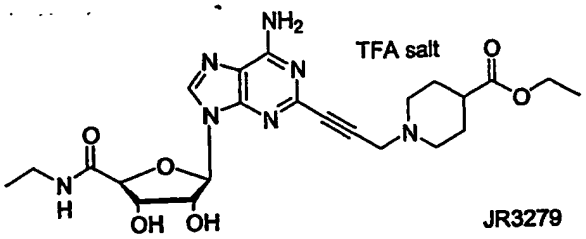
JR3259

Example 37: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4- dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid ethyl ester (JR3269).



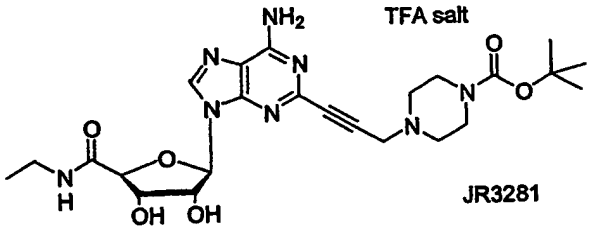
JR3269

Example 38: 1-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-4-carboxylic acid ethyl ester (JR3279).



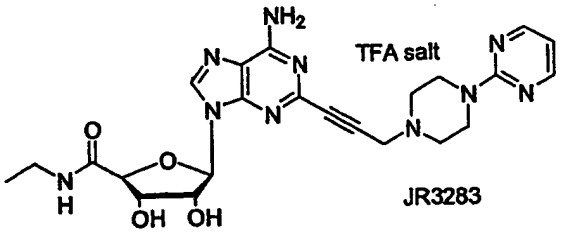
JR3279

Example 39: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4- dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperazine-1-carboxylic acid tert-butyl ester (JR3281).



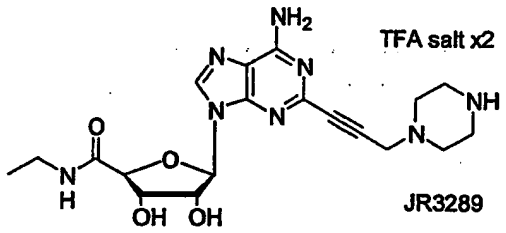
JR3281

Example 40: 5-{6-Amino-2-[3-(4-pyrimidin-2-yl-piperazin-1-yl)-prop-1-ynyl]purin-9-yl}-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3283).



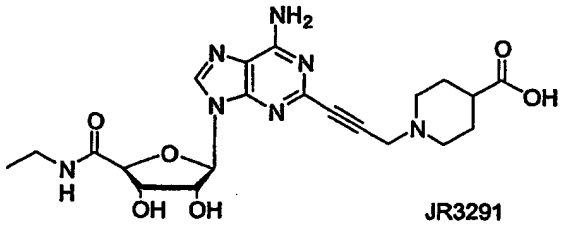
JR3283

Example 41: 5-[6-Amino-2-(3-piperazin-1-yl-prop-1-ynyl)purin-9-yl]-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR3289).



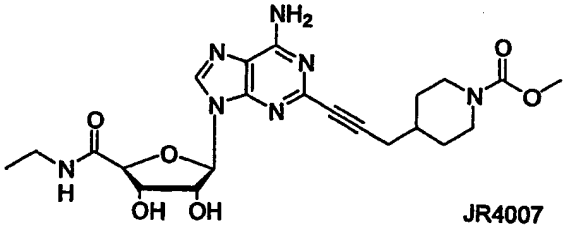
JR3289

Example 42: 1-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-4-carboxylic acid (JR3291).



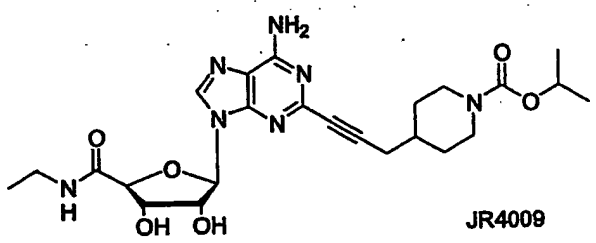
JR3291

Example 43: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid methyl ester (JR4007).



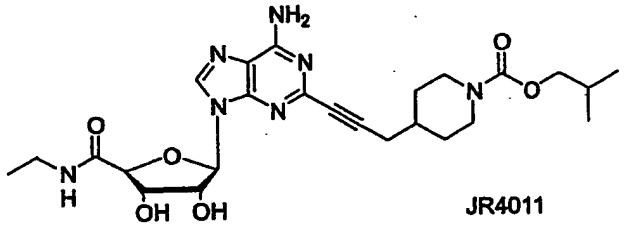
JR4007

Example 44: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid isopropyl ester (JR4009).



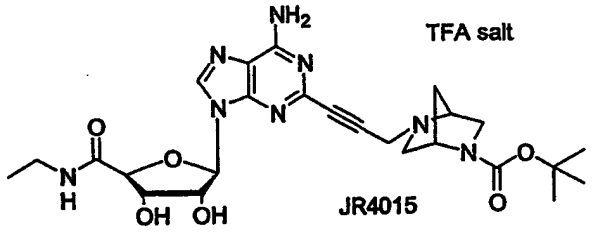
JR4009

Example 45: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperidine-1-carboxylic acid isobutyl ester (JR4011).



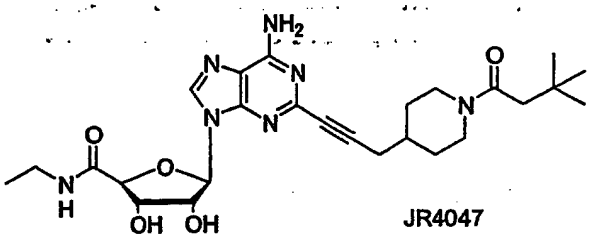
JR4011

Example 46: 5-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]prop-2-ynyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (JR4015).



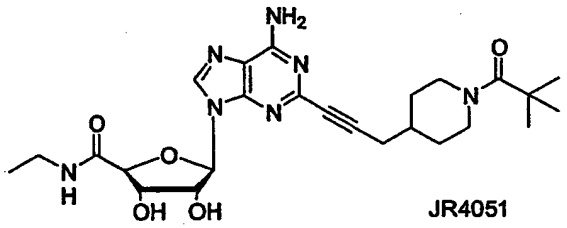
JR4015

Example 47: 5-(6-Amino-2-{3-[1-(3,3-dimethyl-butyryl)-piperidin-4-yl]-prop-1-ynyl}purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR4047).



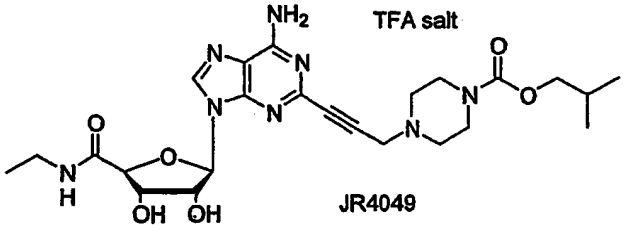
JR4047

Example 48: 5-(6-Amino-2-{3-[1-(2,2-dimethyl-propionyl)-piperidin-4-yl]-prop-1-ynyl}-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR4051).



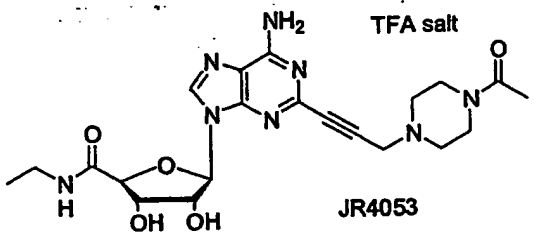
JR4051

Example 49: 4-{3-[6-Amino-9-(5-ethylcarbamoyl-3,4-dihydroxytetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl}-piperazine-1-carboxylic acid isobutyl ester (JR4049).



JR4049

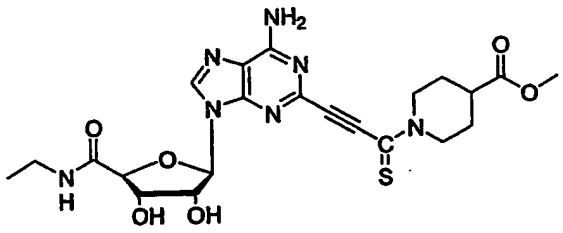
Example 50: 5-{2-[3-(4-Acetyl-piperazin-1-yl)-prop-1-ynyl]-6-amino-purin-9-yl}-3,4-dihydroxytetrahydrofuran-2-carboxylic acid ethylamide (JR4053).



JR4053

Example 51:

The following compounds can be prepared by following the general methods described herein and the appropriate intermediate compounds:



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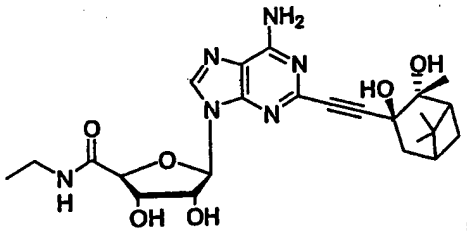

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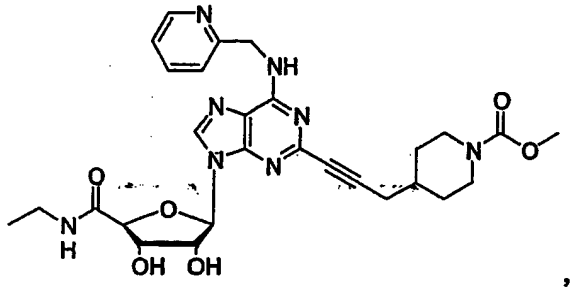

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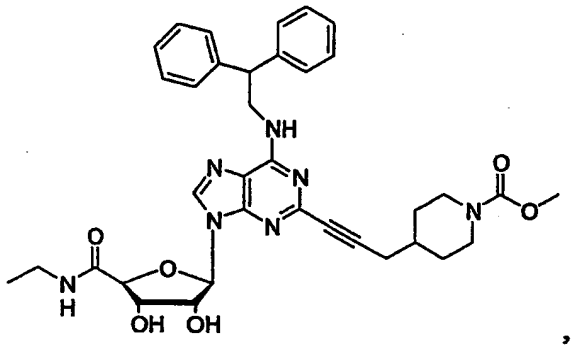

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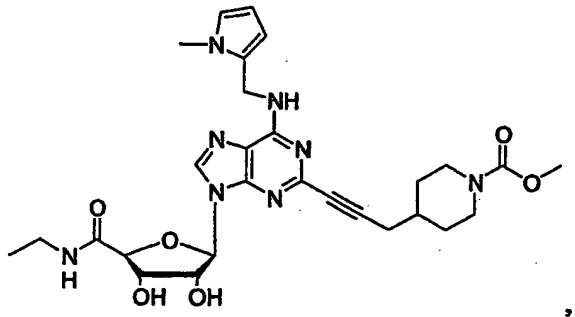

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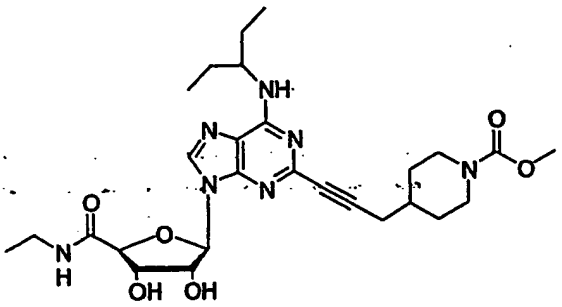
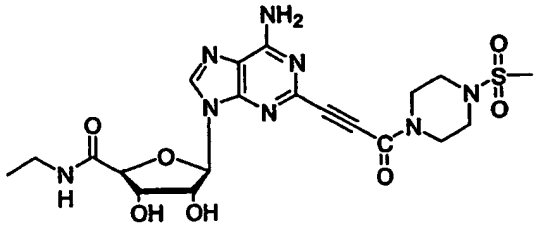




Example 52: Preliminary *in vitro* studies.

The effects of A_{2A}AR agonists, initially WRC-0470 and most recently ATL146e and ATL193, were studied on phagocytic cells *in vitro* and in animal models of acute inflammation. The results indicated that these compounds are potent agonists and provide anti-inflammatory responses, both *in vitro* and *in vivo*. The effect of these compounds on human PMNL (843 receptors per cell) was characterized and quantified A_{2A}ARs. It has been documented that A_{2A}AR agonists increase PMNL intracellular cyclic AMP concentrations while decreasing TNF-enhanced adherence to a fibrinogen-coated surface. The A_{2A}AR agonists reduce TNF-stimulated superoxide release from adherent PMNLs. The super oxide release is completely blocked by the A_{2A}AR antagonist ZM 241385 (ZM). Further, A_{2A}AR agonists reduced PMNL oxidative activity in whole blood assays and decreased degranulation of activated PMNLs adhering to a

biological surface. Rolipram synergistically accentuates all the effects discussed above, on activation of PMNLs. Finally, the protein kinase A inhibitor H-89 completely reversed the inhibitory effect of A_{2A}AR agonists on the PMNL oxidative burst. These findings indicate that A_{2A}AR agonists will modulate inflammation *in vivo* through direct actions on phagocytic cells.

Activation of A_{2A}ARs on human monocytes was also shown to strongly inhibit TNF release. This illustrates the anti-inflammatory action of A_{2A}AR agonists. ATL146e is more potent than CGS21680 in the inhibition of LPS-stimulated human monocyte TNF production, an effect reversed by the selective A_{2A}AR antagonist ZM241385. These data show that A_{2A}AR agonists exert A_{2A}AR-mediated anti-inflammatory effect and reduce TNF production by monocytes.

Example 53: *In vivo* studies.

Dose-response studies: murine model of septic shock

Figure 1, illustrates the mortality of C57BL/6 mice following the intraperitoneal (i.p.) inoculation with *E. coli* 026:B6 LPS (Difco). From these data, a dose of 12.5 mg/kg LPS was selected for murine mortality studies. These studies allow the generation of A_{2A} -KO mice from the same C57BL/6 background (see below). In addition, the model was validated as an excellent model of multisystem organ failure during endotoxemia and septic shock.

A_{2A} AR agonists reduce mortality in a murine model of septic shock.

In these experiments, (n=15-16 per group; LPS 12.5mg/kg), control animals were compared to those treated with ATL146e. The agonist was dosed i.p. at 6-hour intervals for 24 hours, beginning simultaneously with the initial intraperitoneal dose of LPS. The initial dosage of ATL146e utilized was 5 μg/kg; the protection from death (p=0.0002) is illustrated in Figure 2.

At the highest dosages (of ATL146e), complete protection is achieved. All animals surviving to 4 days recover completely. At the highest doses (of ATL146e), survival at 4 days is 100% vs. mortality of 75% in mice receiving control vehicle (phosphate buffered saline i.p.). The effect of an A_{2A}AR agonist on mortality in a septic shock model is orders of magnitude superior to other "anti-inflammatory" agents used in similar models of septic shock, including corticosteroids, anti-LPS monoclonal antibodies, anti-TNF monoclonal antibodies, soluble TNF receptors, and IL-1 receptor antagonists.

ATL146e reduced mortality in a murine model of endotoxin-induced septic shock even after a delay in the onset of therapy. In these experiments, (N=15-16 per group: LPS 12.5 mg/kg), ATL146e was administered at a dose of 5 μg/kg i.p. at six hour intervals at various times after LPS challenge for a total of four doses. The results are illustrated in Figure 3. ATL146e produced protection from death even after a delay of 24 hours following LPS challenge. These experiments are critical since patients with sepsis syndrome and septic shock are often evaluated and treated many hours after the onset of symptoms. A delay of only a few hours eliminated any protective effect in this model with monoclonal antibodies directed against LPS and/ or TNF. Thus, A_{2A} agonists may be beneficial even in far advanced, severe sepsis syndromes.

Example 54: Protective Effects

The protective effect of ATL146e on mortality in the murine model of endotoxin-induced septic shock is specific for the A_{2A} receptor. Two experimental strategies were employed to investigate the specificity of the protective effect observed with ATL146e on mortality and endotoxin-induced shock through the A_{2A} AR receptor. ZM 241385 (ZM), a specific, potent, and highly selective antagonist of the A_{2A}AR is used. As illustrated in Figure 4, ZM alone does not protect mice from death following endotoxin-induced septic

shock. However, when ZM is administered in equimolor concentrations (3 μg/kg) with ATL146e, the protective efficacy of ATL146e is nearly eliminated. Thus, a specific A_{2A} AR antagonist opposes the action of ATL146e and nearly eliminates the survival benefit observed with A_{2A} agonists. In these experiments, both agents were given at six hour intervals for 24 hours beginning 12 hours after LPS challenge.

Homozygous A_{2A} -KO mice. A_{2A} -KO mice have been generated from a heterozygous breeding pair. These mice lack A_{2A}-ARs as confirmed by PCR and by localization studies of A_{2A} -ARs in wild type and A_{2A} -KO mouse brains using a selective A_{2A} AR monoclonal antibody (Figure 5). The mutant A_{2A} AR has been transferred onto a C57BL/6J background using microsattelite-assisted selection. These A_{2A} -KO mice have been used to further examine the specificity of the protective effect of ATL146e in the murine septic shock model (Figure 1). The LPS dose was again 12.5 mg/kg and approximately ten animals were included in each group. ATL was dosed at 5 μg/kg and administered for four doses at six hour intervals beginning at 12 hours following LPS inoculation. As can be seen in Figure 1, the protective effect of ATL146e is completely lost in A_{2A} -KO mice, strongly supporting the specificity of the A_{2A} agonist at the level of the A_{2A} AR

Example 55: Treatment of mice with E. Coli.

Mice were injected with live E. Coli. and treated with an antibiotic (ceftriaxone). The control group of mice were treated with antibiotic alone. All mice were injected with 20 million E. Coli IP at time 0. As indicated the mice were treated once at time 0 with ceftriaxone or with 50 μg/kg ATL146e 8 times at 6 hour intervals. The results are illustrated in Figure 6.

Example 56: Reduction of renal production of IL-6 and RANTES.

Male C57BL/6 mice were injected (i.p.) with E. coli LPS (60 ng) and purified E. coli Shiga toxin-2 (Stx2, 12 ng) at zero hour. ATL-146e or ATL-203 (both 50 μg/kg) was administered i.p. at zero hour. Animals were sacrificed at 6 hrs and the kidneys removed for processing and analysis. IL-6 protein was increased 45-fold by LPS/Stx2 at 6 hr in comparison to the saline control. Both ATL compounds sharply reduced the renal IL-6 levels to approximately 16% of those from mice exposed to LPS/Stx2 (Figure. 7).

Reduction of renal neutrophil accumulation in mice.

Mice received 2.4 ng purified Stx2, i.p. at zero hr. and were treated either with or without ATL-203 compound (i.p.) beginning at zero hr, and every 12 hrs thereafter. Fixed and paraffin-embedded renal samples cut to 3μ thick sections were reacted with neutrophil-specific antibody, etc. prior to analysis. The results illustrated in Figure 9 from kidneys obtained at 48 hrs post-injection of Stx2 show Stx2 caused an 8.5-fold increase in neutrophil positive glomeruli. ATL-203 effectively reduced this to 40 % of the Stx2 positive samples. A similar result was obtained when the 48 hr samples were scored for the average number of neutrophils per high-power field in the renal cortex, excluding neutrophils within the glomeruli. The accumulation of neutrophils in kidneys at 48 hrs is a natural event that leads to further renal damage and that typically contributes to the death of such animals on day 4.

These data demonstrate that the adenosine A_{2A} receptor agonist effectively reduces Stx2-dependent infiltration of neutrophils in kidneys of C57BL/6 mice (Figure 9). This result takes on added significance because the action of ATL-203 is directed at mice exposed to Stx2 alone, i.e. in the absence of LPS.

All cited publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A therapeutic method for treating inflammation caused by pathogenic organisms comprising the administration to a patient in need thereof of an effective amount of an anti-pathogenic agent and an A_{2A} adenosine receptor agonist.

2. A therapeutic method for treating inflammation caused by a viral organism comprising the administration to a patient in need thereof of an effective amount an A_{2A} adenosine receptor agonist.

3. The method of claim 1, wherein the pathogen is a bacteria and the anti-pathogenic agent is an antibiotic.

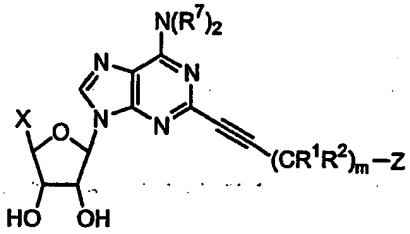
4. The method of claim 1 or 2, wherein the pathogen is a virus and the anti-pathogenic agent is an antiviral agent.

5. The method of claim 1, wherein the pathogen is yeast or fungus and the anti-pathogenic agent is an antifungal agent.

6. The method of claim 3, wherein the inflammation is caused by E. Coli.

7. The method of claim 3, wherein wherein the bacteria causes hemolytic uremic syndrome.

8. The method of any of claims 1 to 7, wherein the A_{2A} adenosine receptor agonist is a compound having formula (I):



(I)

wherein

Z is $CR^3R^4R^5$ or NR^4R^5;

each R^1 is independently hydrogen, halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, heterocycle, hetrocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^bR^cNC(=O)O-$, $R^aOC(=O)N(R^b)-$, R^bR^cN-, $R^bR^cNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^bR^cNC(=O)N(R^b)-$, $R^bR^cNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)-$, $R^aS(=O)_2-$, $-N=NR^b$, or $-OPO_2R^a$;

each R^2 is independently hydrogen, halo, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, heterocycle, heterocycle(C_1-C_8)alkylene-, aryl, aryl(C_1-C_8)alkylene-, heteroaryl, or heteroaryl(C_1-C_8)alkylene-; or

R^1 and R^2 and the atom to which they are attached is C=O, C=S or $C=NR^d$;

R^4 and R^5 together with the atoms to which they are attached form a saturated or partially unsaturated, mono-, bicyclic- or aromatic ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms optionally comprising 1, 2, 3, or 4 heteroatoms selected from non-peroxide oxy (-O-), thio (-S-), sulfinyl (-SO-), sulfonyl $(-S(O)_2-)$ or amine $(-NR^b-)$ in the ring;

wherein any ring comprising R^4 and R^5 is substituted with from 1 to 14 R^6 groups; wherein each R^6 is independently halo, $-OR^a$, $-SR^a$,

$(C_1$-$C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_1$-$C_8)$cycloalkyl, $(C_6$-$C_{12})$bicycloalkyl, heterocycle or hetrocycle $(C_1$-$C_8)$alkylene-, aryl, aryl $(C_1$-$C_8)$alkylene-, heteroaryl, heteroaryl$(C_1$-$C_8)$alkylene-, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^bR^cNC(=O)O$-, $R^aOC(=O)N(R^b)$-, R^bR^cN-, $R^bR^cNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^bR^cNC(=O)N(R^b)$-, $R^bR^cNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $-NNR^b$,$-OPO_2R^a$, or two R^6 groups and the atom to which they are attached is C=O, C=S or; two R^6 groups together with the atom or atoms to which they are attached can form a carbocyclic or heterocyclic ring;

R^3 is hydrogen, halo, $-OR^a$, $-SR^a$, $(C_1$-$C_8)$alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, $(C_3$-$C_8)$cycloalkyl, heterocycle, hetrocycle$(C_1$-$C_8)$alkylene-, aryl, aryl$(C_1$-$C_8)$alkylene-, heteroaryl, heteroaryl$(C_1$-$C_8)$alkylene-, $-CO_2R^a$, $R^aC(=O)O$-, $R^aC(=O)$-, $-OCO_2R^a$, $R^bR^cNC(=O)O$-, $R^aOC(=O)N(R^b)$-, R^bR^cN-, $R^bR^cNC(=O)$-, $R^aC(=O)N(R^b)$-, $R^bR^cNC(=O)N(R^b)$-, $R^bR^cNC(=S)N(R^b)$-, $-OPO_3R^a$, $R^aOC(=S)$-, $R^aC(=S)$-, $-SSR^a$, $R^aS(=O)$-, $R^aS(=O)_2$-, $-NNR^b$, $-OPO_2R^a$; or if the ring formed from CR^4R^5 is aryl or hetreroaryl or partially unsaturated then R^3 can be absent;

each R^7 is independently hydrogen, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$cycloalkyl, aryl or aryl$(C_1$-$C_8)$alkylene, heteroaryl, heteroaryl$(C_1$-$C_8)$alkylene-;

X is $-CH_2OR^a$, $-CO_2R^a$, $-OC(O)R^a$, $-CH_2OC(O)R^a$, $-C(O)NR^bR^c$, $-CH_2SR^a$, $-C(S)OR^a$, $-OC(S)R^a$, $-CH_2OC(S)R^a$ or $-C(S)NR0^bR^c$ or $-CH_2N(R^b)(R^c)$;

wherein any of the alkyl, cycloalkyl, heterocycle, aryl, or heteroaryl, groups of R^1, R^2, R^3, R^6 and $R^7$is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from

the group consisting of halo, $-OR^a$, $-SR^a$, (C_1-C_8)alkyl, cyano, nitro, trifluoromethyl, trifluoromethoxy, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, heterocycle or hetrocycle(C_1-C_8)alkylene-, aryl, aryloxy, aryl (C_1-C_8)alkylene-, heteroaryl, heteroaryl(C_1-C_8)alkylene-, $-CO_2R^a$, $R^aC(=O)O-$, $R^aC(=O)-$, $-OCO_2R^a$, $R^bR^cNC(=O)O-$, $R^aOC(=O)N(R^b)-$, R^bR^cN-, $R^bR^cNC(=O)-$, $R^aC(=O)N(R^b)-$, $R^bR^cNC(=O)N(R^b)-$, $R^bR^cNC(=S)N(R^b)-$, $-OPO_3R^a$, $R^aOC(=S)-$, $R^aC(=S)-$, $-SSR^a$, $R^aS(=O)_p-$, $R^bR^cNS(O)_p-$, $N=NR^b$, and $-OPO_2R^a$;

wherein any (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, (C_6-C_{12})bicycloalkyl, (C_1-C_8)alkoxy, (C_1-C_8)alkanoyl, (C_1-C_8)alkylene, or heterocycle, is optionally partially unsaturated;

each R^a, R^b and R^c is independently hydrogen, (C_1-C_8)alkyl, or (C_1-C_8)alkyl substituted with 1-3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, amino acid, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; or R^b and R^c, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and

R^d is hydrogen or (C_1-C_6)alkyl;

m is 0 to about 8 and p is 0 to 2;

or a pharmaceutically acceptable salt thereof.

9. The method of claim 8, wherein R^1 is hydrogen, -OH, $-CH_2OH$, -OMe, -OAc, $-NH_2$, -NHMe, $-NMe_2$ or –NHAc.

10. The method of claims 8 or 9, wherein R^1 is hydrogen, -OH, -OMe, -OAc, $-NH_2$, -NHMe, $-NMe_2$ or -NHAc.

11. The method of any of claims 8 to 10, wherein R^1 is hydrogen, OH, OMe, or NH_2.

12. The method of any of claims 8 to 11, wherein R^1 is hydrogen, OH, or NH_2.

13. The method of any of claims 8 to 12, wherein R^1 is hydrogen or OH.

14. The method of claim 8, wherein R^2 is hydrogen, (C_1-C_8)alkyl, cyclopropyl, cyclohexyl or benzyl.

15. The method of any of claims 9 to 14, wherein R^2 is hydrogen, methyl, ethyl or propyl.

16. The method of any of claims 8 to 15, wherein R^2 is hydrogen or methyl.

17. The method of any of claims 8 to 16, wherein R^2 is hydrogen.

18. The method of claim 8, wherein R^1, R^2 and the carbon atom to which they are attached is carbonyl (C=O).

19. The method of claim 8, wherein R^3 is hydrogen, OH, OMe, OAc, NH_2, NHMe, NMe_2 or NHAc.

20. The method of any of claims 8 to 19, wherein R^3 is hydrogen, OH, OMe, or NH_2.

21. The method of any of claims 8 to 20, wherein R^3 is hydrogen, OH, or NH_2.

22. The method of claim 21, wherein R^3 is hydrogen or OH.

23. The method of claim 8, wherein the ring comprising R^4, R^5 and the atom to which they are connected is cyclopentane, cyclohexane, piperidine, dihydro-pyridine, tetrahydro-pyridine, pyridine, piperazine, decaline, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine,

pyrazine, imidazole, dihydro-imidazole, imidazolidine, pyrazole, dihydro-pyrazole, and. pyrazolidine.

24. The method of any of claims 8 to 23, wherein the ring comprising R^4, R^5 and the atom to which they are connected is cyclopentane, cyclohexane, piperidine, dihydro-pyridine, tetrahydro-pyridine, pyridine, piperazine, tetrahydro-pyrazine, dihydro-pyrazine, pyrazine, dihydro-pyrimidine, tetrahydro-pyrimidine, hexahydro-pyrimidine, pyrazine, imidazole, dihydro-imidazole, imidazolidine, pyrazole, dihydro-pyrazole, and. pyrazolidine.

25. The method of any of claims 8 to 24, wherein the ring comprising R^4 and R^5 and the atom to which they are connected is, cyclohexane, piperidine or piperazine.

26. The method of claim 8, wherein R^6 is $(C_1\text{-}C_8)$alkyl, or substituted $(C_1\text{-}C_8)$alkyl, $-OR^a$, $-CO_2R^a$, $R^aC(=O)$-, $R^aC(=O)O$-, R^bR^cN-, $R^bR^cNC(=O)$-, or aryl.

27. The method of any of claims 8 to 26, wherein R^6 is $(C_1\text{-}C_8)$alkyl, $-OR^a$, $-CO_2R^a$, $R^aC(=O)$-, RaC(=O)O-, R^bR^cN-, $R^bR^cNC(=O)$-, or aryl.

28. The method of any of claims 8 to 27, wherein R^6 is methyl, ethyl, butyl, OH, OR^a, $-CO_2R^a$, $R^aC(=O)$-, $OC(=O)CH_2CH_3$, $-CONR^bR^c$, NR^bR^c or phenyl.

29. The method of claim 28, wherein R^6 is OH, OMe, methyl, ethyl, t-butyl, $-CO_2R^a$, $-CONR^bR^c$, OAc, NH_2, NHMe, NMe_2, NHEt or $N(Et)_2$.

30. The method of claim 29, wherein R^6 is methyl, ethyl, t-butyl, phenyl, $-CO_2R^a$ $-CONR^bR^c$, or $-(=O)CR^a$.

31. The method of claim 30, wherein R^6 is methyl, ethyl, $-CO_2R^a$ $-CONR^bR^c$, or OAc.

32. The method of claim 31, wherein R^6 is $-(CH_2)_{1-2}OR^a$, $-(CH_2)_{1-2}C(=O)OR^a$, $-(CH_2)_{1-2}OC(=O)R^a$, $-(CH_2)_{1-2}C(=O)R^a$, $-(CH_2)_{1-2}OCO_2R^a$, $-(CH_2)_{1-2}NHR^a$, $-(CH_2)_{1-2}NR^bR^c$, $-(CH_2)_{1-2}OC(=O)NHR^a$, or $-(CH_2)_{1-2}OC(=O)NR^bR^c$.

33. The method of any of claims 8 to 32, wherein R^6 is $-CH_2OH$, $-CH_2OAc$, $-CH_2OCH_3$, $-CH_2C(=O)OCH_3$, $-CH_2OC(=O)CH_3$, $-CH_2C(=O)CH_3$, $-CH_2OCO_2CH_3$, $-CH_2NH(CH_3)$, or $-(CH_2)_{1-2}N(CH_3)_2$.

34. The method of any of claims 8 to 33, wherein R^6 is $-CH_2OH$, $-CH_2OAc$, $-C(=O)OCH_3$, $-C(=O)CH_3$, OCO_2CH_3 $-OCO_2CH_3$, $-CH_2NH(CH_3)$, or $-(CH_2)_{1-2}N(CH_3)_2$.

35. The method of claim 8, wherein number of R^6 groups substituted on the R^4R^5 ring is from 1 to about 4.

36. The method of claim 8, wherein R^a and R^b are independently hydrogen, (C_1-C_4)alkyl, aryl or aryl(C_1-C_8)alkylene.

37. The method of claim 36, wherein R^a and R^b are independently hydrogen, methyl or ethyl, phenyl or benzyl.

38. The method of claim 37, wherein R^a is (C_1-C_8)alkyl.

39. The method of claim 38, wherein R^a is methyl, ethyl, propyl or butyl.

40. The method of claim 39, wherein R^a is, methyl, ethyl, i-propyl, i-butyl or tert-butyl.

41. The method of claim 40, wherein R^b and R^c and the atom to which they are attached form a ring.

42. The method of claim 41, wherein R^7 is hydrogen, alkyl, aryl or aryl(C_1-C_8)alkylene.

43. The method of claim 42, wherein R^7 is hydrogen, methyl or ethyl, phenyl or benzyl.

44. The method of claim 43, wherein R^7 is H, or methyl.

45. The method of claim 44, wherein $N(R^7)_2$ is amino, methylamino, dimethylamino; ethylamino; pentylamino, diphenylethylamino, pyridylmethylamino, diethylamino or benzylamino.

46. The method of claim 45, wherein -$N(R^7)_2$ is amino, methylamino, dimethylamino; ethylamino; diethylamino or benzylamino.

47. The method of claim 46, wherein $N(R^7)_2$ is amino, or methylamino.

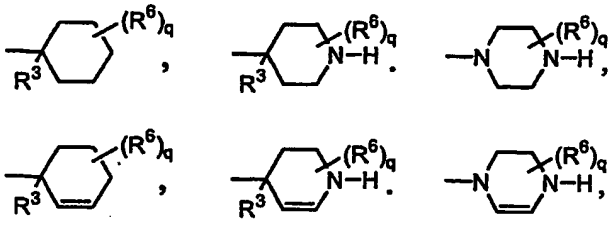
48. The method of claim 47, wherein X is -CH_2OR^a, -CO_2R^a, -$OC(O)R^a$, -$CH_2OC(O)R^a$, -$C(O)NR^bR^c$.

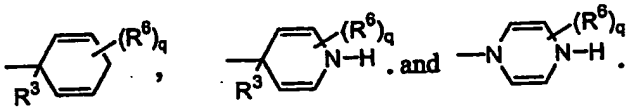
49. The method of claim 48, wherein X is is -CH_2OR^a or -$C(O)NR^bR^c$.

50. The method of claim 49, wherein X is -CH_2OH or -$C(O)NHCH_2CH_3$.

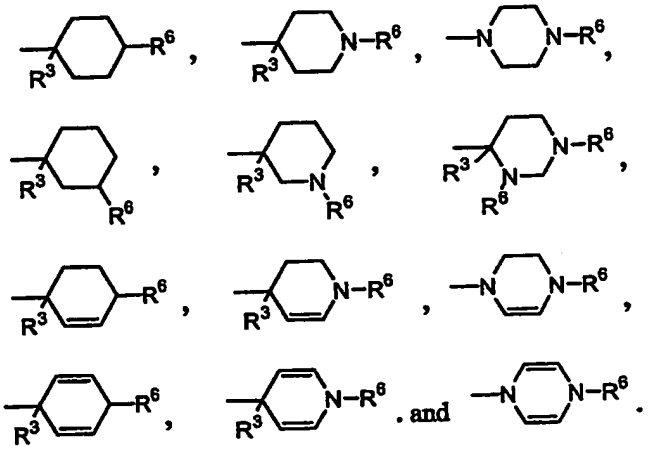
51. The method of claim 50, wherein m is 0, 1, or 2.

52. The method of claim 51, wherein the rings comprising R^4, R^5 and the atom to which they are connected are selected from the group consisting of:





53. The method of claim 52, wherein the rings comprising R^4, R^5 and the atom to which they are connected are selected from the group consisting of:



54. The method of claim 53, wherein the ring comprising R^4 and R^5 is 2-methylcyclohexane, 2,2-dimethylcyclohexane, 2-phenylcyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butylcyclohexane, 3-methylcyclohexane, 3,3-dimethylcyclohexane, 4-methylcyclohexane, 4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butylcyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane. 4-cyclohexanecarboxyic acid, 4-cyclohexanecarboxyic acid esters, or 4-methyloxyalkanoyl-cyclohexane.

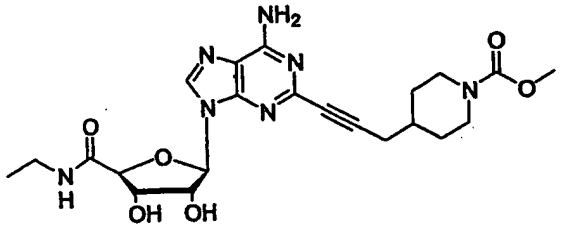
55. The method of claim 54, wherein the ring comprising R^4 and R^5 is 4-piperidine, 4-piperidene-1-carboxylic acid, 4-piperidine-1-carboxylic

acid methyl ester, 4-piperidine-1-carboxylic acid ethyl ester, 4-piperidine-1-carboxylic acid propyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester, 1-piperidine, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-carboxylic acid ethyl ester, 1-piperidine-4-carboxylic acid propyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester , 1-piperidine-4-carboxylic acid methyl ester, 3-piperidine, 3-piperidene-1-carboxylic acid, 3-piperidine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butyl ester, 1,4-piperazine, 4-piperazine-1-carboxylic acid, 4-piperazine-1-carboxylic acid methyl ester, 4-piperazine-1-carboxylic acid ethyl ester, 4-piperazine-1-carboxylic acid propyl ester, 4-piperazine-1-carboxylic acid tert-butylester, 1,3-piperazine, 3-piperazine-1-carboxylic acid, 3-piperazine-1-carboxylic acid methyl ester, 3-piperazine-1-carboxylic acid ethyl ester, 3-piperazine-1-carboxylic acid propyl ester, 3-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-3-carboxylic acid methyl ester, 1-piperidine-3-carboxylic acid ethyl ester, 1-piperidine-3-carboxylic acid propyl ester or 1-piperidine-3-caboxylic acid tert-butyl ester.

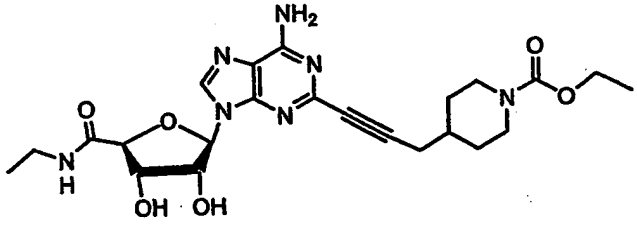
56. The method of claim 55, wherein the ring comprising R^4 and R^5 is 2-methyl cyclohexane, 2,2-dimethylcyclohexane, 2- phenyl cyclohexane, 2-ethylcyclohexane, 2,2-diethylcyclohexane, 2-tert-butyl cyclohexane, 3-methyl cyclohexane, 3,3-dimethylcyclohexane, 4-methyl cyclohexane, 4-ethylcyclohexane, 4-phenyl cyclohexane, 4-tert-butyl cyclohexane, 4-carboxymethyl cyclohexane, 4-carboxyethyl cyclohexane, 3,3,5,5-tetramethyl cyclohexane, 2,4-dimethyl cyclopentane, 4-piperidine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic acid tert-butyl ester 4-piperidine, 4-piperazine-1-carboxylic acid methyl ester, 4-piperidine-1-carboxylic

acid tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, 1-piperidine-4-caboxylic acid tert-butyl ester , tert-butylester, 1-piperidine-4-carboxylic acid methyl ester, or 1-piperidine-4-caboxylic acid tert-butyl ester, 3-piperidine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butyl ester, 3-piperidine, 3-piperazine-1-carboxylic acid methyl ester, 3-piperidine-1-carboxylic acid tert-butylester, 1-piperidine-3-carboxylic acid methyl ester, 1-piperidine-3-caboxylic acid tert-butyl ester.

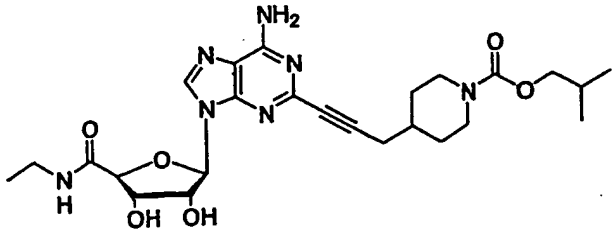
57. A compound of claim 8, having the formula:



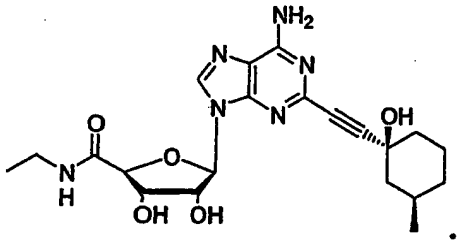
58. A compound of claim 8, having the formula:



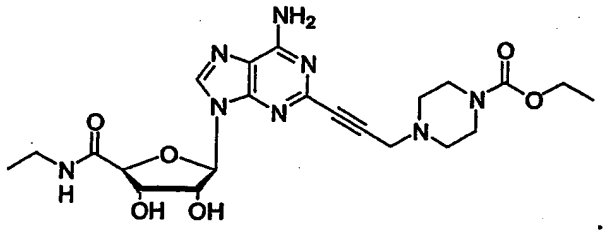
59. A compound of claim 8, having the formula:



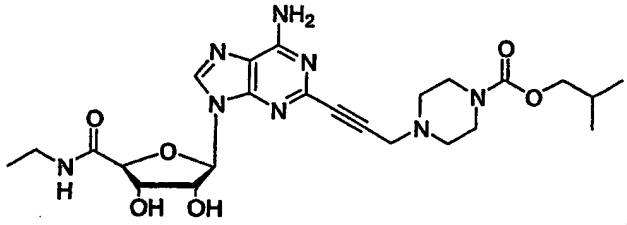
60. A compound of claim 8, having the formula:



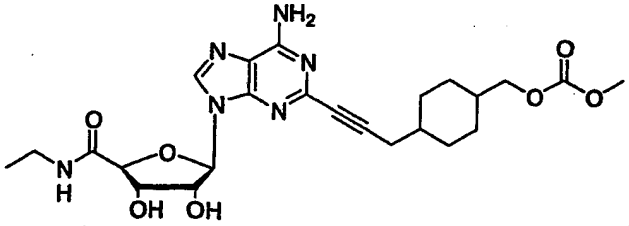
61. A compound of claim 8, having the formula:



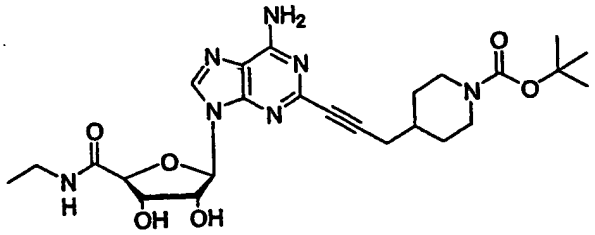
62. A compound of claim 8, having the formula:



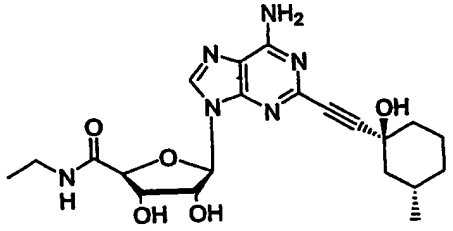
63. A compound of claim 8, having the formula:



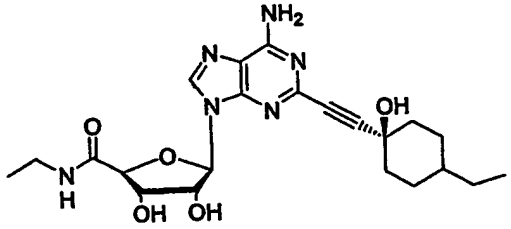
64. A compound of claim 8, having the formula:



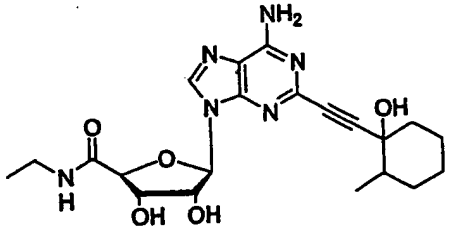
65. A compound of claim 8, having the formula:



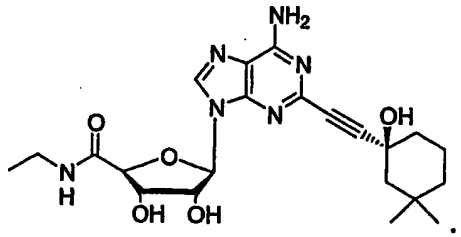
66. A compound of claim 8, having the formula:



67. A compound of claim 8, having the formula:



68. A compound of claim 8, having the formula:



69. The method of claim 8, wherein Z is $CR^3R^4R^5$; each R^1, R^2 and R^3 is hydrogen; R^4 and R^5 together with the carbon atom to which they are attached form a cycloalkyl ring having 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms; and

wherein the ring comprising R^4 and R^5 is substituted with $-(CH_2)_{0-6}$-Y; where Y is $-CH_2OR^a$, $-CO_2R^a$, $-OC(O)R^a$, $-CH_2OC(O)R^a$, $-C(O)NR^bR^c$, $-CH_2SR^a$, $-C(S)OR^a$, $-OC(S)R^a$, $-CH_2OC(S)R^a$ or $C(S)NR^bR^c$ or $-CH_2N(R^a)(R^b)$;

each R^7 is independently hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, aryl or aryl(C_1-C_8)alkylene;

X is $-CH_2OR^a$, $-CO_2R^a$, $-OC(O)R^a$, $-CH_2OC(O)R^a$, $-C(O)NR^bR^c$, $-CH_2SR^a$, $-C(S)OR^a$, $-OC(S)R^a$, $-CH_2OC(S)R^a$ or $C(S)NR^bR^c$ or $-CH_2N(R^b)(R^c)$;

each R^a, R^b and R^c is independently hydrogen, (C_1-C_8)alkyl, or (C_1-C_8)alkyl substituted with 1-3 (C_1-C_8)alkoxy, (C_3-C_8)cycloalkyl, (C_1-C_8)alkylthio, amino acid, aryl, aryl(C_1-C_8)alkylene, heteroaryl, or heteroaryl(C_1-C_8)alkylene; or R^b and R^c, together with the nitrogen to which they are attached, form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring; and

m is 0 to about 6;

or a pharmaceutically acceptable salt thereof.

70. The method of claim 8, wherein the A_{2A} adenosine receptor agonist is ATL-146e, AB-1, AB-3 or JR-3213.

71. The method of claim 70, wherein the A_{2A} adenosine receptor agonist is ATL-146e.

72. The method of claims 1, 2, 3, 4, or 5, further comprising administering a Type IV phosphodiesterase inhibitor in combination with the compound of formula (I).

73. The method of claim 72 wherein Type IV phosphodiesterase inhibitor is rolipram.

74. Use of a compound of claim 8, to prepare a medicament for treating inhibition of inflammation caused by pathogenic toxins.

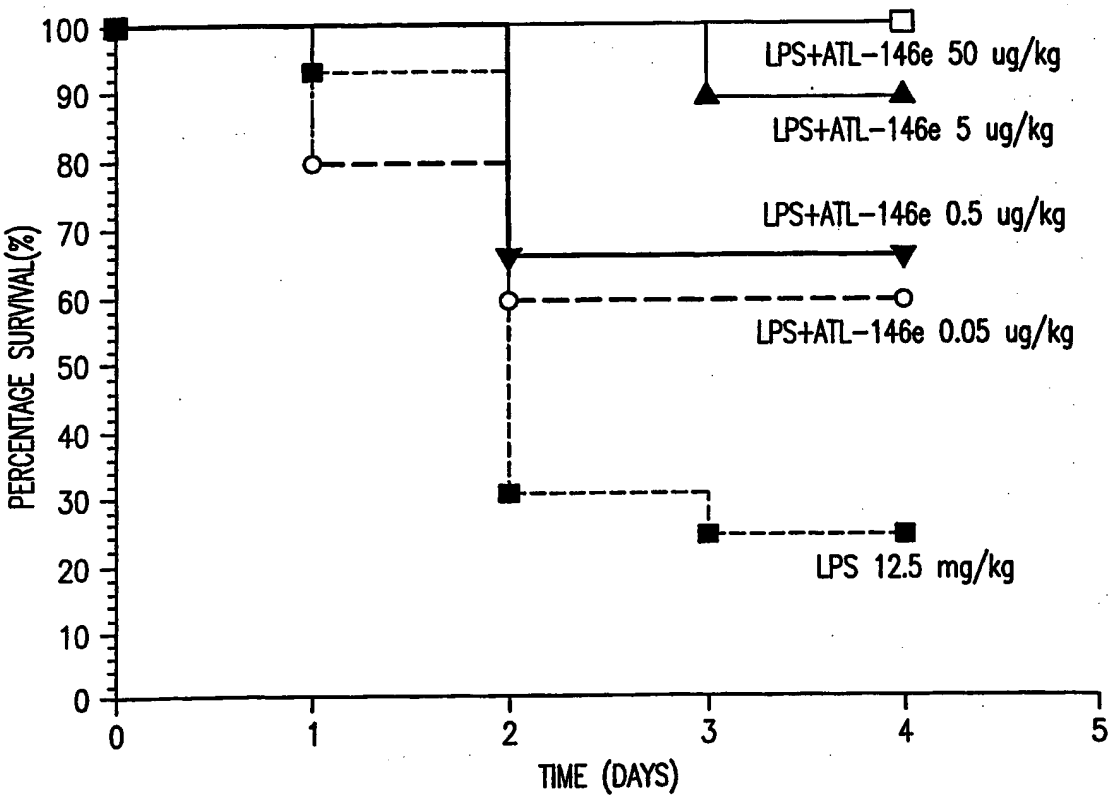

100
90
80
70
60
50
40
30
20
10
0
PERCENTAGE SURVIVAL(%)
0
1
2
3
4
5
TIME (DAYS)
LPS+ATL-146e 50 ug/kg
LPS+ATL-146e 5 ug/kg
LPS+ATL-146e 0.5 ug/kg
LPS+ATL-146e 0.05 ug/kg
LPS 12.5 mg/kg

FIG. 1

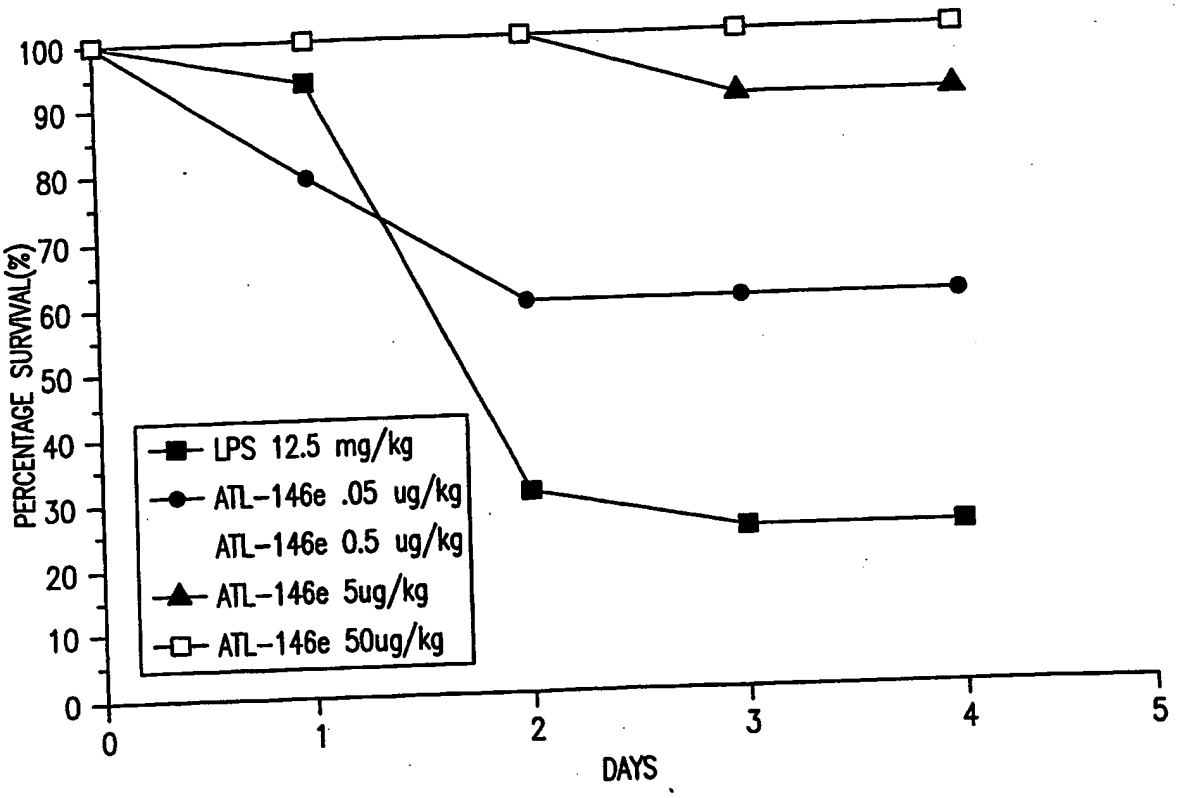

PERCENTAGE SURVIVAL(%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
DAYS
LPS 12.5 mg/kg
ATL-146e .05 ug/kg
ATL-146e 0.5 ug/kg
ATL-146e 5ug/kg
ATL-146e 50ug/kg

FIG. 2

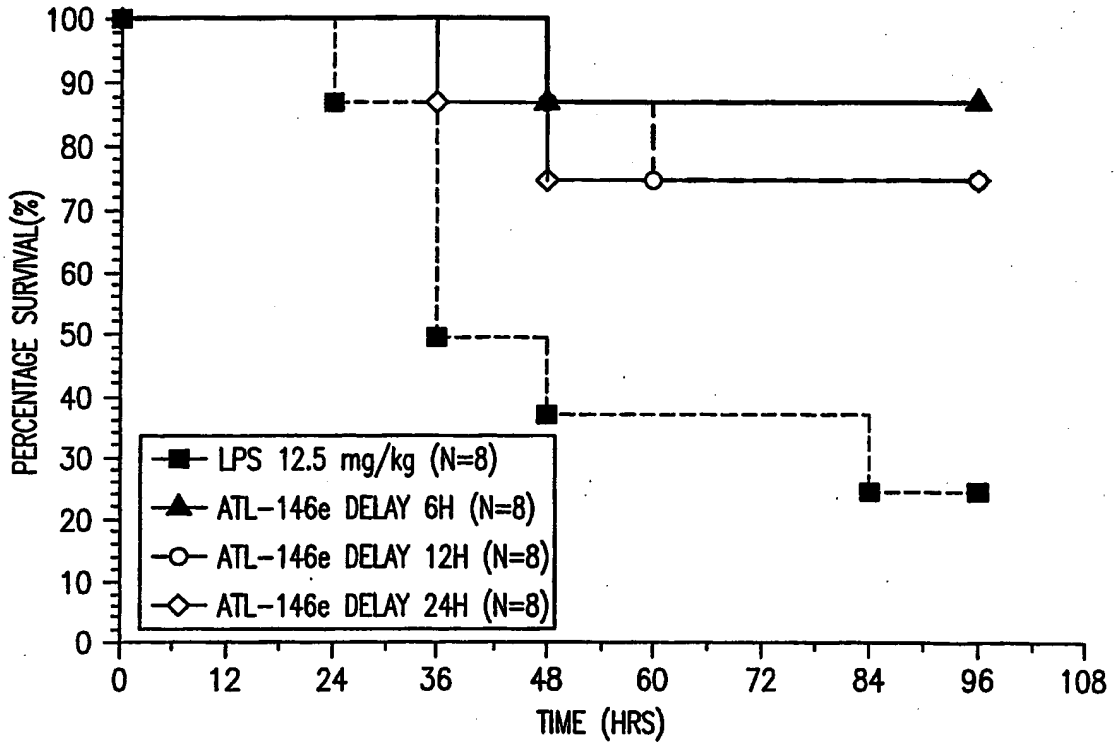

100
90
80
70
60
50
40
30
20
10
0
PERCENTAGE SURVIVAL(%)
0
12
24
36
48
60
72
84
96
108
TIME (HRS)
LPS 12.5 mg/kg (N=8)
ATL-146e DELAY 6H (N=8)
ATL-146e DELAY 12H (N=8)
ATL-146e DELAY 24H (N=8)

FIG. 3

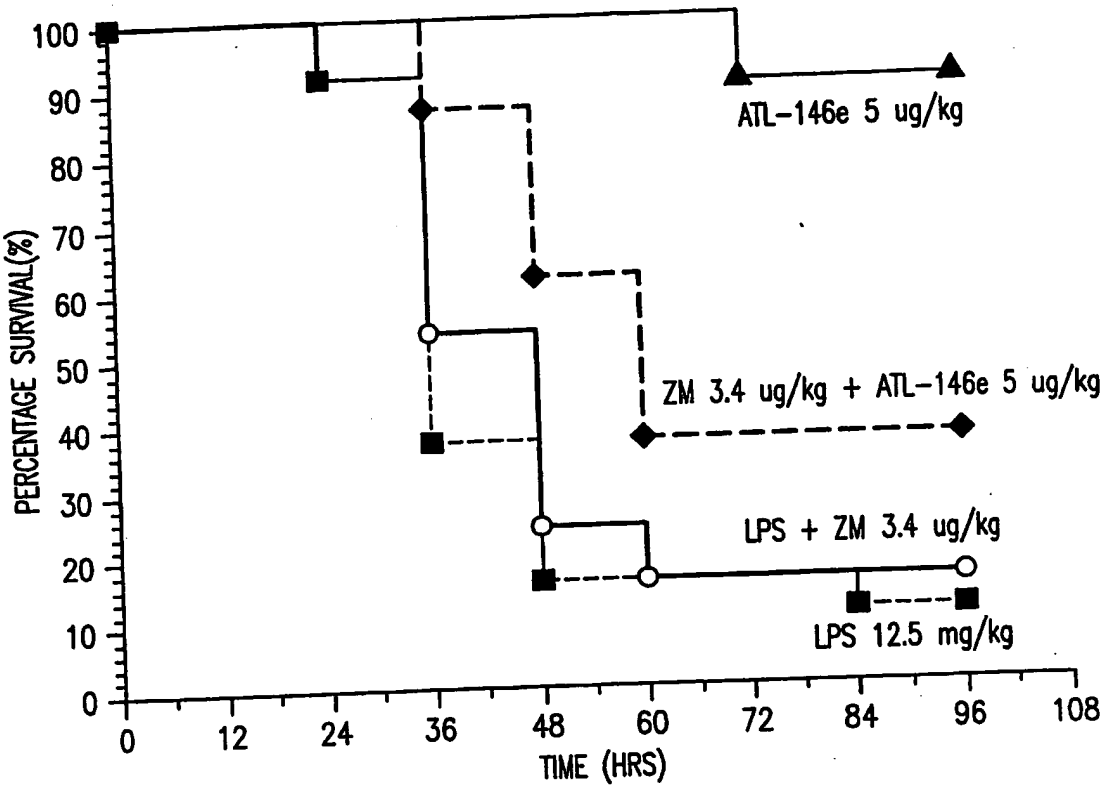

100
90
80
70
60
50
40
30
20
10
0
PERCENTAGE SURVIVAL(%)
0
12
24
36
48
60
72
84
96
108
TIME (HRS)
ATL-146e 5 ug/kg
ZM 3.4 ug/kg + ATL-146e 5 ug/kg
LPS + ZM 3.4 ug/kg
LPS 12.5 mg/kg

FIG. 4

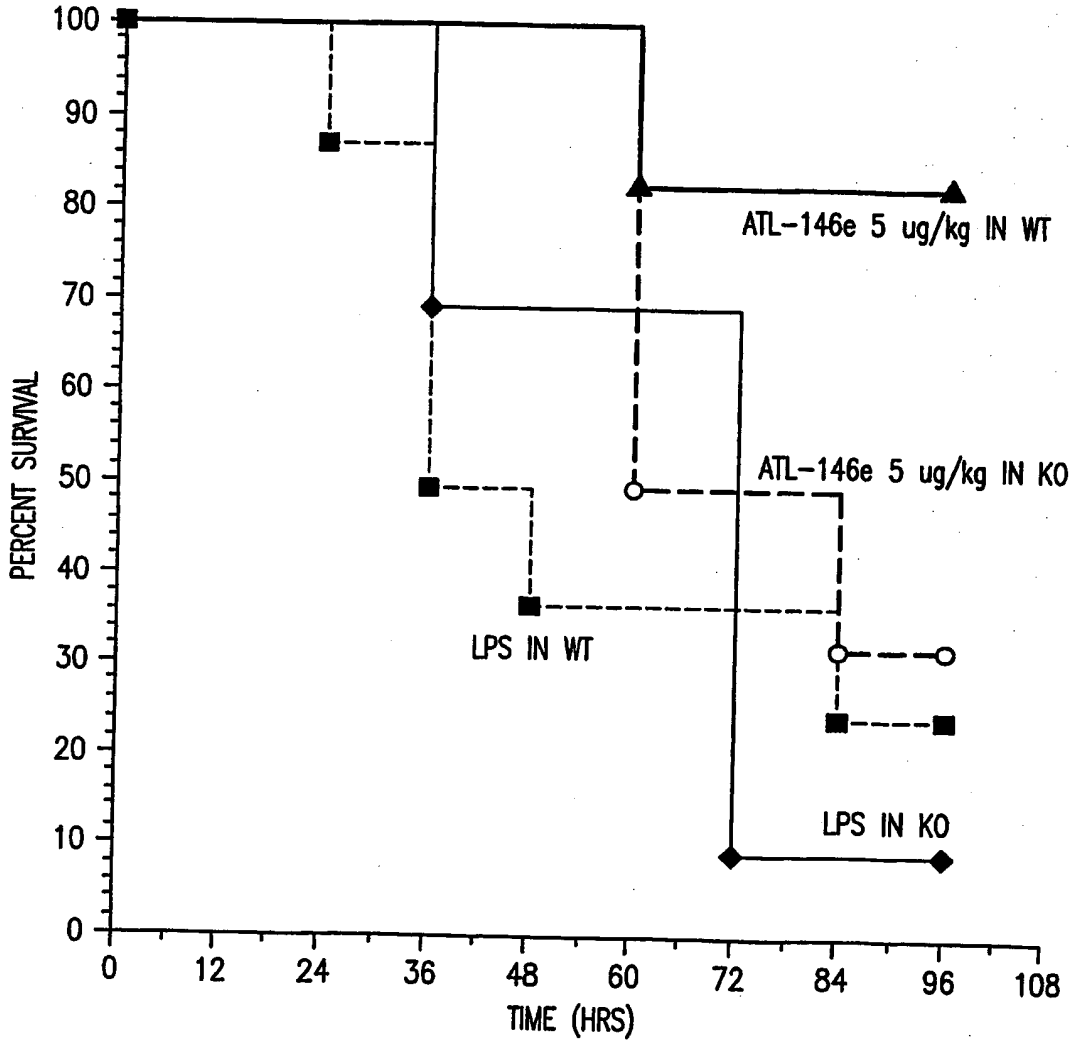

100
90
80
70
60
50
40
30
20
10
0
PERCENT SURVIVAL
0
12
24
36
48
60
72
84
96
108
TIME (HRS)
ATL-146e 5 ug/kg IN WT
ATL-146e 5 ug/kg IN KO
LPS IN WT
LPS IN KO

FIG. 5

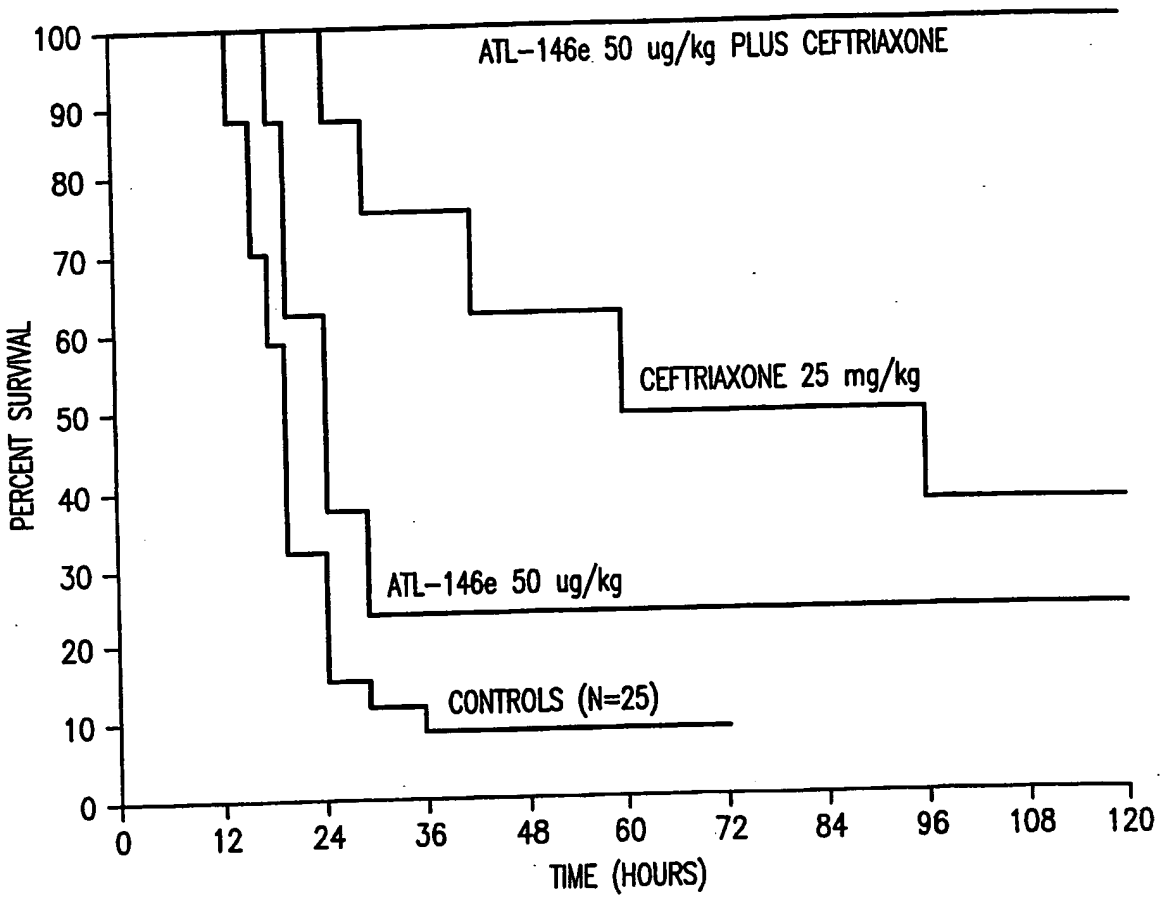

ATL-146e 50 ug/kg PLUS CEFTRIAXONE
CEFTRIAXONE 25 mg/kg
ATL-146e 50 ug/kg
CONTROLS (N=25)
PERCENT SURVIVAL
TIME (HOURS)
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
84
96
108
120

FIG. 6

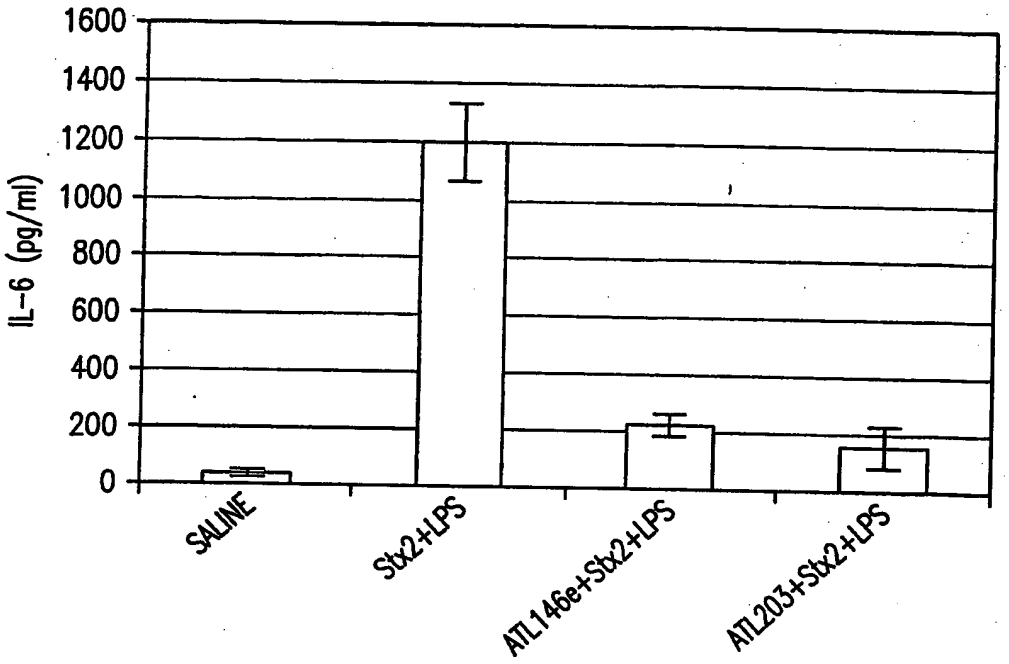

1600
1400
1200
1000
800
600
400
200
0
IL-6 (pg/ml)
SALINE
Stx2+LPS
ATL146e+Stx2+LPS
ATL203+Stx2+LPS

FIG. 7

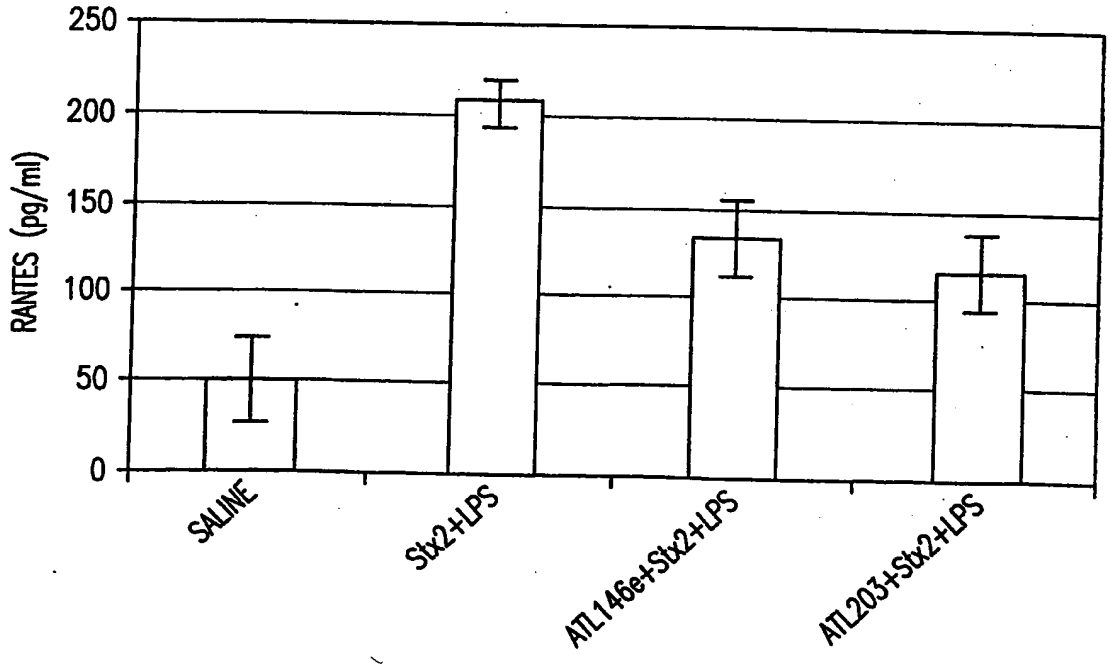

250
200
150
100
50
0
RANTES (pg/ml)
SALINE
Stx2+LPS
ATL146e+Stx2+LPS
ATL203+Stx2+LPS

FIG. 8

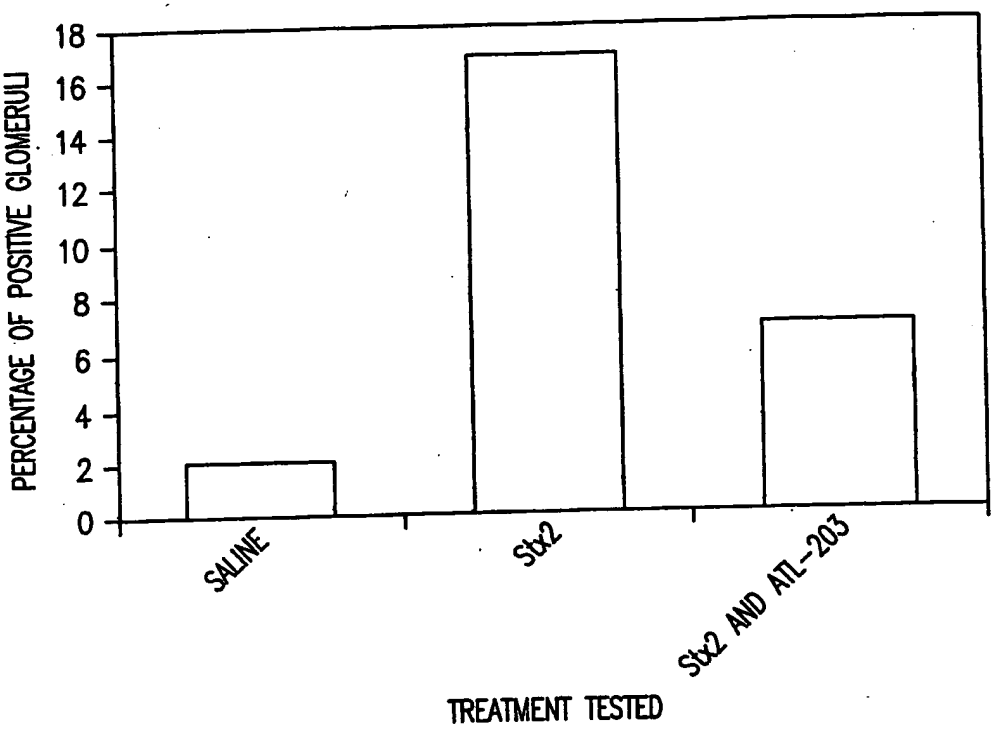

PERCENTAGE OF POSITIVE GLOMERULI
18
16
14
12
10
8
6
4
2
0
SALINE
Stx2
Stx2 AND ATL-203
TREATMENT TESTED

FIG. 9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/11146

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 72799 A (LINDEN JOEL M ;UNIV VIRGINIA (US); SAREMBOCK IAN J (US); SULLIVAN) 7 December 2000 (2000-12-07) claims 1-3 page 13, line 27 - line 32 page 20, line 17	1-17, 19-25, 35, 42-53, 55,72-74
Y	US 5 877 180 A (LINDEN JOEL M ET AL) 2 March 1999 (1999-03-02) claims 1-3 figure 3	1-74
Y	WO 99 34804 A (UNIV VIRGINIA) 15 July 1999 (1999-07-15) claims 1,3 page 12, line 11 - line 32	1-74

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 July 2003	25/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Beranová, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/11146

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SULLIVAN G W ET AL: "NEUTROPHIL A2A ADENOSINE RECEPTOR INHIBITS INFLAMMATION IN A RAT MODEL OF MENINGITIS: SYNERGY WITH THE TYPE IV PHOSPHODIESTERASE INHIBITOR, ROLIPRAM" JOURNAL OF INFECTIOUS DISEASES, CHICAGO, IL, US, vol. 180, no. 5, November 1999 (1999-11), pages 1550-1560, XP000978330 ISSN: 0022-1899 * page 1558, left-hand column, last paragraph *	1-74
Y	BUSTER B(A) ET AL: "The effect of adenosine receptor agonists on neutrophil pleocytosis and blood-brain barrier pathophysiology in experimental bacterial meningitis" PROGRAM AND ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, XX, XX, vol. 37, 1997, page 39 XP002104913 * abstract *	1-74
Y	SULLIVAN G W ET AL: "ROLE OF A2A ADENOSINE RECEPTORS IN INFLAMMATION" DRUG DEVELOPMENT RESEARCH, NEW YORK, NY, US, vol. 45, no. 3/4, November 1998 (1998-11), pages 103-112, XP000978332 ISSN: 0272-4391 page 109, left-hand column, paragraph 3	1-74
Y	SULLIVAN GW ET AL: "The specific type IV phosphodiesterase inhibitor rolipram combined with adenosine reduces tumor necrosis factor-alpha-primed neutrophil oxidative activity" INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, ELMSFORD,NY, US, vol. 17, no. 10, 1995, pages 793-803, XP002104914 ISSN: 0192-0561 * abstract *	1-74
Y	US 6 350 735 B1 (MONAGHAN SANDRA MARINA) 26 February 2002 (2002-02-26) claims 1,22	1-71,74
Y	WO 01 94368 A (STEPHENSON PETER THOMAS ;PFIZER LTD (GB); MANTELL SIMON JOHN (GB);) 13 December 2001 (2001-12-13) claims 1,47,48,51	1-71,74

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/11146

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 - 73 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 - 7 and 72 relate to a compound defined by reference to a desirable characteristic or property, namely "A2A adenosine receptor agonist", "anti-pathogenic agent" and "type IV phosphodiesterase inhibitor". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I) and rolipram.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/11146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0072799 A	07-12-2000	AU 5294100 A	18-12-2000
		WO 0072799 A2	07-12-2000
		US 6514949 B1	04-02-2003
US 5877180 A	02-03-1999	US 2002082240 A1	27-06-2002
		US 6514949 B1	04-02-2003
WO 9934804 A	15-07-1999	AU 2108299 A	26-07-1999
		CA 2317093 A1	15-07-1999
		EP 1044004 A1	18-10-2000
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		WO 9934804 A1	15-07-1999
		US 2002082240 A1	27-06-2002
		US 6514949 B1	04-02-2003
US 6350735 B1	26-02-2002	AT 238336 T	15-05-2003
		AU 7548800 A	23-04-2001
		BG 106569 A	29-12-2002
		BR 0011776 A	12-03-2002
		CA 2387531 A1	19-04-2001
		CN 1358192 T	10-07-2002
		CZ 20021223 A3	14-05-2003
		DE 60002356 D1	28-05-2003
		EE 200200193 A	16-06-2003
		EP 1220863 A1	10-07-2002
		HU 0203483 A2	28-02-2003
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		NO 20021692 A	10-04-2002
		TR 200200985 T2	21-10-2002
WO 0194368 A	13-12-2001	AU 6053701 A	17-12-2001
		BG 107216 A	30-05-2003
		BR 0111263 A	17-06-2003
		EP 1292604 A1	19-03-2003
		WO 0194368 A1	13-12-2001
		NO 20025821 A	04-02-2003
		US 2002058641 A1	16-05-2002